UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

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MEETING

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Thursday, April 24, 1997

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The meeting took place in the Versailles Rooms I and II, Holiday Inn -- Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Paul D. Brown, M.D., Chairman, presiding.

PRESENT:

PAUL W. BROWN, M.D., Chairman

WILLIAM FREAS, Ph.D., Executive Secretary

LINDA A. DETWILER, D.V.M., Member

LEON FAITEK, Member

BARBARA W. HARRELL, M.P.A., Member

DAVID G. HOEL, Ph.D., Member

PRESENT (Continued):

WILLIAM D. HUESTON, D.V.M., Ph.D., Member

KATHERINE O'ROURKE, Ph.D., Member

RAYMOND P. ROOS, M.D., Member

LAWRENCE B. SCHONBERGER, M.D., Member

GILBERT C. WHITE, II, M.D., Member

SIDNEY M. WOLFE, M.D., Member

TEMPORARY VOTING MEMBERS PRESENT:

ERIC A. DECKER, Ph.D.

HANS P. RIEMANN, D.V.M., Ph.D.

FAC TEMPORARY INDUSTRY LIAISON PRESENT:

J. MICHAEL DUNN, Ph.D.

DONALD P. WRATHALL, Ph.D.

GUEST SPEAKERS PRESENT:

ROBERT ROHWER, Ph.D.

REINHARD SCHRIEBER

GUEST EXPERT PRESENT:

GERALD M. WISEMAN

FDA PRESENTER PRESENT:

DAVID ASHER, M.D.

ALSO PRESENT:

JOHN B. BAILEY, Ph.D.

YUAN-YUAN CHIU, M.D.

KIKI HELLMAN, Ph.D.

JOHN HONSTEAD, D.V.M.

ALSO PRESENT (Continued):

GEORGE MASTON

BERT MITCHELL, D.V.M.

PETER SAFIR, J.D.

JOHN VANDERVEEN, Ph.D.

CAROL VINCENT, M.S.

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:06 a.m.)

DR. FREAS: Good morning. Again, I'm Bill Freas. I'm the Executive Secretary for this Advisory Committee, and I would like to welcome you to the second day of the Transmissible Spongiform Encephalopathies Advisory Committee.

Today's entire meeting will be open to the public.

The conflict of interest statement that was read into the public record yesterday remains in effect today, and it pertains to all items that were on the agenda as handed out yesterday.

I would now like to turn the microphone over to our Chairman, Dr. Paul Brown.

CHAIRMAN BROWN: Thank you, Dr. Freas.

Our last educational speaker who you heard yesterday, Dr. Rohwer, is not yet present, but we have two agenda items that precede him, and perhaps he'll be here before they're finished.

The first item is recitation of the charge and questions for this Committee, and Dr. David Asher in the FDA will read them to us so that you may know what questions we are being asked to try and answer at the conclusion of this meeting.

Dr. Asher.

DR. ASHER: Thank you, Dr. Brown.

I'm David Asher from FDA's Center for Biologics Evaluation and Research.

What I want to do this morning is to repeat briefly the charge and questions that Dr. Hellman put to the TSE Advisory Committee yesterday. In fact, my remarks are really a reduction and reprise of hers, but they may serve to orient those here who missed yesterday's session and to concentrate attention on gelatin safety issues of greatest concern to the FDA, that is, with respect to spongiform encephalopathies.

First, I'd like to remind you of some of the background. In December of 1993, FDA requested that bovine derived materials originating from animals born or living in BSE countries not be used to manufacture FDA regulated products intended for humans.

In the summer of the following year, FDA issued guidance noting that it did not object to the use of bovine derived materials from BSE countries in manufacture of pharmaceutical grade gelatin, although it considered it prudent to obtain those materials from non-BSE countries, what we might call the gelatin

exemption.

That decision reflected a conclusion that available evidence does not suggest transmission of TSE by gelatin, which was based on an assessment that manufacturing conditions were likely to inactivate the infectious agent.

Though not explicitly stated, FDA authorities may also have relied to a considerable degree on a perceived species barrier between cattle and humans, which was widely believed or perhaps hoped to protect humans from BSE, as it has probably protected us from infection from scrapie arising in sheep.

However, for several reasons the FDA must now reconsider the gelatin exemption and other issues relevant to BSE. Most dramatic was the recognition of new variant, Creutzfeldt-Jakob disease, in the U.K. and France, which reduced, if not eliminated, our confidence in protection afforded to humans by the species barrier. Actually confidence in that species barrier was greatly shaken by the report in 1990 of feline spongiform encephalopathy occurring in cats in the United Kingdom, something that had never been seen in the pre-BSE era.

Second, as you heard yesterday, FDA has

not been provided with scientific evidence showing that gelatin processing has removed all TSE infectivity from starting materials.

Finally, there was concern that some source materials for gelatin might contain bovine neural tissue, and of course, imported gelatin was of special concern in that regard.

Concern about the safety of gelatin was not restricted to regulatory authorities at the FDA. For example, here are two recent recommendations on gelatin from the World Health Organization, one in 1996 and the other just this past month, and you will note that there is a subtle increased emphasis on the safe sourcing of gelatin raw materials. In April of '96, countries should not permit tissues that are likely to contain the BSE agent to enter any food chain, human or animal, but gelatin in the food chain is considered to be safe if produced by a manufacturing process utilizing production conditions that significantly inactivate any residual infectivity that may have been present.

And then last month, careful selection of source materials is the most important criterion for the safety of medicinal products. Raw materials used for the production of gelatin should be sourced from

safe materials.

In addition, the manufacturing process utilizing production conditions which have been demonstrated to significantly remove or inactivate TSE infectivity in source tissues should be used. If this is done, gelatin is considered safe for all purposes.

The implication was that sources of gelatin should be free of BSE agent, and the process should remove most infectivity potentially present in the starting material.

Last year's OIE chapter noted that byproducts, such as gelatin collagen tallow, are considered to be safe if produced by processes under study which inactivate any residual BSE infectivity, and the implication there was that the process should remove all BSE infectivity potentially present in the starting material.

And finally, a recent release from the Multi-disciplinary Scientific Committee of the European Commission meeting on April 3rd of this year. The technical treatment conditions set out in Commission Decision 96, et cetera, of 11 June '96, a decision which eased the ban on exported British gelatin, provided stricter heat processing rules were respected, do not adequately guarantee the

inactivation of the BSE agent. Only noninfected primary bovine material can insure a totally safe gelatin, and in press accounts of the same date stated that the European Union had not actually allowed any exports of gelatin made from British beef because British manufacturers have not fulfilled the preconditions of the 1996 decision.

Although the FDA is not obligated to adopt WHO or EC recommendations, we are committed to international efforts to harmonize regulatory requirements, and we greatly respect the opinions of international deliberative bodies, especially where the issues concern protection of public health.

And finally, as John Gray told us yesterday, regulations of our sister agency, USDA, do not reflect a high level of confidence in the safety of gelatin prepared from source materials potentially contaminated with the BSE agent.

To remind you, in December 1991, USDA regulation held that gelatin from BSE countries is not to come in contact with ruminants. Importers of gelatins from BSE countries must obtain veterinary permits for importation and transportation of controlled materials, organisms and vectors, and in an explanatory note two years later, USDA stated that

gelatin derived from ruminants from BSE countries poses a risk of spreading BSE to ruminants.

So taken together, we concluded that FDA's exemption for gelatin, the exemption from restrictions on sourcing from BSE countries, must now be reconsidered, as well as other issues related to the safety of gelatin with regard to TSE agents, and this meeting was convened.

And now to remind you of the topics that the Committee might consider in its deliberations. One, of course, the sources of starting material and of finished gelatin in byproducts.

Second, gelatin processing, the potential of the various methods that we heard discussed yesterday to remove or inactivate the TSE agents.

Third, validation of processing, evidence that processing eliminated the TSE agents.

And, last, assessment of the overall risk to humans and perhaps to animals posed by gelatin and gelatin byproducts, including the source of the gelatin and the process and also the potential for exposure to be sufficient to transmit an infection.

And features, among others, that might be considered would be the probability of exposure to a human being; the amounts of infectious agent that are

likely to be present; the frequency of the exposure.

Of great concern to several centers is the route of exposure. CBER's main concern is with injectable gelatin present in vaccines and other injectable products.

Devices is concerned with implantable gelatin that remain in the body for a prolonged period of time.

The Center for Food Safety and Applied Nutrition is concerned with cosmetics, with topicals which are applied to the skin, health skin and to abraded or diseased skin. What does the route of exposure -- what role does that play in assessing risk for human beings?

And finally, susceptibility of human beings to infection.

In addition, the various centers have provided members of the committee with a list of other specific issues related to these topics, issues of special concern to them, and you have them in your packets.

The questions to be answered I've reduced a little bit to four, two on sourcing and two on processing. The single most important question, of course, is this: does current scientific evidence

justify continuing to exempt gelatin from restrictions recommended by FDA for other bovine derived materials from BSE countries?

And we ask the voting members of the Committee to be polled on this question.

Second, sourcing. If gelatin and gelatin byproducts are no longer to be exempted from FDA BSE restrictions, what level of restriction is sufficient to reduce the risk appropriately?

And we provided a list of possible options: restrict gelatin from all countries on USDA's BSE list; restrict gelatin from countries where BSE has been highly prevalent, but not from countries where only a few cases have been recognized.

Allow gelatins from establishments in BSE countries preparing product from certified non-BSE source materials, for example, from bones or hides verified to contain or certified to contain no skulls or spine, originating only from cattle born and residing in non-BSE countries, perhaps adding a requirement that they not have been fed ruminant derived protein.

Allow gelatin from certified BSE-free herds in BSE countries, and Dr. Hsiao yesterday noted the problem in that there's no standard definition of

what constitutes a BSE-free herd, and USDA may well be reconsidering what constitutes a BSE-free country.

And finally, the Committee might prefer to suggest some other level of control, but we would request that each TSE Advisory Committee member try to express an opinion on this issue.

Then we have two questions. I combined two of Dr. Hellman's questions into this on gelatin processing and the validation of that processing. I combined the questions concerning preferred or essential methods for eliminating infectivity from gelatin.

Which, if any, specific gelatin processing procedure is preferred or essential to assure optimal inactivation of any contaminating TSE agent? And we invite TSE members to express their opinions on this issue.

And the last question: what criteria should be considered in designing gelatin process validation studies and analyzing the results of such studies? And the members are invited to express their opinions on this issue as well.

I want to close by repeating Dr. Wykoff's remark yesterday, that in addition to addressing the questions that I have just repeated, the TSE Advisory

Committee should feel free to make any other recommendations or suggestions on these or related issues.

I also want to encourage public comments on these issues. We allowed ample time for that yesterday and again this morning, and we welcome open discussion of these issues.

CHAIRMAN BROWN: Thank you, Dr. Asher.

I made a couple of notes while you were talking, and I had one questions for the manufacturers, and I'm going to ask it now simply because they may not have done the arithmetic or may not have the answer immediately, and they could try and figure it out while we're doing other things, and that question is -- and I hope it wasn't asked yesterday and I didn't catch the answer -- and I'll phrase it this way:

One gram of gelatin represents what weight of bones or of skin, and translated even further, how does that translate into the number of cows or partial cows that would make -- in other words, would one cow make a gram of gelatin?

This is the kind of number that I'd like to have available, and the same for skin.

We now have the opportunity to have an

open public hearing in that again this morning, as yesterday morning, if anybody in the room would like to come forward, address the Committee with questions or comments, now is the time to do it.

If there are such questions or comments, the person who has them should come to a live microphone, identify themselves, and we shall listen.

Yes, sir.

DR. VANDERVEEN: I'm John Vanderveen from the Food and Drug Administration.

It was pointed out to me that yesterday I indicated that the importation of gelatin from France for food was made entirely from pork skins or from cattle hide. I neglected to say that for edible gelatins that are used for pharmaceutical applications, for soft and hard capsules, is coming from France, from both the Type B lined and/or limited hide gelatin and Type A acid bone gelatin.

So, indeed, from France there is some, and France was the only BSE country that U.S. manufacturers are bringing in from a BSE country.

I also indicated, and I want to emphasize that gelatin from other sources, from foreign processors, of course, come into the United States which are derived from bone.

I didn't want to leave the impression that no bone gelatin is coming in from a BSE country by a U.S. manufacturer. I hope that is clear now.

CHAIRMAN BROWN: Thank you very much.

Dr. Schrieber.

MR. SCHRIEBER: I'd like just to give you the answer on your question because our American colleagues might have a problem because what I said yesterday. They are not degreasing the bones here. So they don't have the real relationship between the fresh bone from the cattle and the final product because they are buying from the slaughterhouse or from the meat packer already the degreased bones.

But the general rule is one kilogram gelatin comes from one cattle. About 25 kilograms of fresh bones, including fat, water, minerals, and everything, gives at the end of the process one kilogram of gelatin.

CHAIRMAN BROWN: And that is just considering bones, not skin?

MR. SCHRIEBER: With regard to the hides, you would have the same quantity once again. So if you would use the hide from the same cattle, you would have another kilogram gelatin made from these hides, yes.

CHAIRMAN BROWN: So as it turns out, in the processing the usable hide from one cow will produce ten kilos of gelatin?

MR. SCHRIEBER: No, the usable hide would make one kilogram of gelatin, and the usable bones would make another kilogram of gelatin.

CHAIRMAN BROWN: Right. So if you used the skin and bones, if I may say so --

MR. SCHRIEBER: Of the same cattle --

CHAIRMAN BROWN: -- you would have two kilograms of gelatin.

MR. SCHRIEBER: Yes, but it is basically in the reality absolutely unlikely that you would have the hide and the bones of the same cattle at the same moment at the same gelatin plant because of what I said yesterday. The hides are going first to the tannery, and the hide of a cattle might show up at a totally different place for gelatin manufacture, and the bones are showing up.

CHAIRMAN BROWN: Right. Oh, I understand that.

And for pigs?

MR. WISEMAN: Same order of magnitude.

MR. SCHRIEBER: Rather the same, yeah.

CHAIRMAN BROWN: One pig, about?

MR. WISEMAN: Yeah.

CHAIRMAN BROWN: One kilo?

MR. WISEMAN: A little less than a kilo.

CHAIRMAN BROWN: But it's like we talk about the incidence of CJD, one per million. It's a good round number to remember, and so we have one animal produces one kilo of -- yes, that's correct. One animal translates to one kilo of gelatin.

Okay. At this point, are there any other questions?

(No response.)

CHAIRMAN BROWN: Okay. At this point ordinarily we would have asked Dr. Rohwer to speak, to give us his reading of what validation studies in this field should be and what they have been. I am told that there is a horrendous accident on Connecticut Avenue which may conceivably have or be the reason for his not being here, and rather than just take an indefinite break for the next ten, 15 or 50 minutes, what he was going to talk about and probably will when he gets here is validation.

This Committee has been charged, as you have just heard, also with considering questions of sourcing so that the information that he is going to give us this morning is irrelevant to that

consideration, and what I am, therefore, going to do is go on and have the Committee address all of the questions that have to do with sourcing.

Perhaps it would be useful, Dave, to put the slide in which those questions were listed, and we can consider each one in turn.

So, Committee members, it's voting time.

Yes, Dr. Riemann.

DR. RIEMANN: I'm Hans Riemann, University of California.

We have heard about the effect of the area's processing procedures used in guaranteeing manufacturing.

PARTICIPANT: It's very difficult to hear.

DR. RIEMANN: We have heard about the different processes used in manufacturing of gelatin and the impacts they have or might have on the prions causing BSE and other diseases, and we have heard that certain precautions are being taken in the selection of raw material.

My question is: how are these things being verified? Do companies use something like a hazard procedure, hazard analysis and critical control points which have been induced by the food processing industry in this country for the last 30 years? Do

they apply for and get ISO 9000 certification, which would provide them a similar degree of verification?

I don't know. So I ask these questions. I don't know who's going to answer.

CHAIRMAN BROWN: Well, I don't either. Is there anybody who feels that he has expertise to answer this questions?

Anybody in the FDA? Will?

DR. HUESTON: I attempted to answer similar questions yesterday about sourcing, and the best that I could make of the answer was that those processes were not in place as it related to sourcing.

Is that --

DR. RIEMANN: Well, I don't think it answers the question completely. I think in the traditional hazard procedure --

CHAIRMAN BROWN: Dr. Riemann, would you state again the specific question that you are seeking an answer to?

DR. RIEMANN: The specific question is that the manufacturers of gelatin, they have certain rules and regulations they follow with respect to the source of the raw material. They have certain processes they follow when they manufacture the gelatin, and my question is: how is this being

verified and made available for the agencies who should have access to it? Do they use hazard analysis and critical control point procedure which is commonly used in the food processing industry?

It's now being mandated for seafood in the United States. It's going to be mandated for slaughterhouses, or do the use the alternative, which to me would be to apply for certification on international standards, ISO 9002, probably the best one? And my question is: are these things being done or is there something else being put in place which would have the same effect?

CHAIRMAN BROWN: Okay. So the question is, I think, clearly in the realm of the Department of Agriculture, and it involves appropriate and effective surveillance and controls to insure that whatever regulations are in place are being followed.

Who wishes to respond? And I'm talking now about Department of Agriculture people. I can't think of any other authority that would be able to provide that information. Surely someone in this room from the Department of Agriculture wishes to step forward.

(Laughter.)

DR. DETWILER: I'm still confused on the

nature of the question on HACCP. You're absolutely right that the HACCP concept will be put into place in the slaughterhouses, but the sourcing from U.S. sources as far as ante mortem and post mortem inspection, that's twofold because that does happen in the slaughter plants, and when they source from there, they can receive certificates from the Department of Agriculture that the animals have passed both ante mortem and post mortem inspections.

At the ports Dr. Gray told us yesterday as far as products coming in, there's over 2,000 inspectors at the ports to inspect the materials coming in. As far as the sources for any animal products, they would be prohibited, and they come under special permits that would prohibit it and that go to specific facilities.

Is that the nature of your question on the checks and balances with the sources, Dr. Riemann?

DR. RIEMANN: Well, I think in general the companies that apply hazard -- now, slaughterhouses, of course, are a special example -- but let's say a food processing company or other manufacturing company, for most of them the incoming raw material will represent a critical control point, and we will try to get assurance that they stay within critical

limits either by specifications for the raw material, which the supplier must live up to or require that the supplier has a raw hazard plan in place, acceptable hazard plan in place.

I think the slaughterhouse with the red meat or poultry is the most basic example.

CHAIRMAN BROWN: Yes, Dr. Dunn.

DR. DUNN: I think I can add a point of clarification here. You mentioned international certification. I can at least speak definitively for our company, Kind & Knox and Eastman Gelatine, today that we are ISO 9001 certified, which is the highest level of that type of certification.

I can't definitively speak for the whole industry at this point. We'd have to clarify that point if there's further interest there.

CHAIRMAN BROWN: Is there any other input to this question?

Yes, a question from the floor?

MR. MASTON: My name is George Maston. I'm the President of the Gelatin Manufacturers Institute of America, to which we all belong here.

I wanted to expand on Mike's comment that all of the plants with one exception, which is a porcine plant, are ISO certified in the United States.

CHAIRMAN BROWN: Did you want to dig a little further, Dr. Riemann, or is that --

DR. RIEMANN: No, I think this is important information.

CHAIRMAN BROWN: Dr. Schrieber?

MR. SCHRIEBER: I have to add the same statement for Europe. Basically all gelatin plants are ISO 9001 or 9002. All gelatin plants are under constant veterinary control by public veterinarians because we are a food processor. So we are controlled constantly, not like a slaughterhouse where you have already the veterinarian on the floor every day, but at least once a month a veterinary comes. He's checking the files, the laboratory results. He walks through the plant, looks about the sanitary conditions.

So we are under constant control by regulatory bodies.

CHAIRMAN BROWN: Yes. A question again?

MS. VINCENT: This is one of the points I think I didn't make too well yesterday, that we don't have a good regulatory handle on gelatin. We would like to see these types of certifications as an incoming specification, but we just don't have the regulatory handle to put that out.

CHAIRMAN BROWN: Meaning that most of the regulation is self-imposed?

MS. VINCENT: No, that for pharmaceutical purposes gelatin is compendial, and so we can't add to any requirements for that because of the Paper Work Reduction Act.

CHAIRMAN BROWN: Well, now you're beginning to get out of my field. I don't -- there are plenty of regulators in the room, but --

(Laughter.)

DR. HUESTON: In a word, Paul, I think the answer to your question is there are no regulations covering gelatin.

CHAIRMAN BROWN: Right. Okay. There are no regulations covering gelatin. What leverage do you have?

For example, we know that there may not be any regulations with respect to the import of Product X, but the USDA can itself prevent Product X from coming in simply by refusing to issue an import permit.

MS. VINCENT: That's true. Let Dr. Chiu amplify that.

DR. CHIU: Yuan-Yuan Chiu, Center for Drugs.

I would like to amplify what Carol has said. Gelatin has historically to be considered last. That's generally recognized as safe. Therefore, the agency historically has not required detail processing information or additional requirements beyond compendial.

However, if there are safety issues related even to excipients for manufacturing a product, a drug product, the agency does have the authority to require additional information from specific manufacturers.

That's why we have been working with the Gelatin Manufacturers Association of the United States, and we have requested the manufacturers to match the validation protocols with the validation data for us to evaluate.

So I do believe we have the authority to require the information for the safety, the purpose of the drug.

CHAIRMAN BROWN: Yes, Dr. Meicoff (phonetic).

DR. VANDERVEEN: Vanderveen.

CHAIRMAN BROWN: I'm sorry. Vanderveen.

DR. VANDERVEEN: Let me expound relative to foods. As stated, gelatin is considered GRAS

because, of course, it was in prior to the 1957 Food Additive Act, in addition to the Food, Drug, and Cosmetic Act. It has been in the process of being affirmed as GRAS and has not been affirmed as GRAS, as such, but that's not a major issue.

We could, if it considered necessary, go back and deal with the gelatin as a food additive and put requirements on it.

CHAIRMAN BROWN: Before you go any further, Dr. Vanderveen, I assume that GRAS is not or gelatin is not considered GRAS because grass is eaten by cows.

DR. VANDERVEEN: Yes. Okay.

CHAIRMAN BROWN: This is an acronym; is that correct?

DR. VANDERVEEN: "Generally recognized as safe" is the category in the Food, Drug and Cosmetic Act, and that is the acronym GRAS that's being put there.

I just wanted to indicate we have plenty of authority to take care of it if there is considered a necessity to take any further steps in regulating the safety of gelatin.

CHAIRMAN BROWN: Thank you.

Yes, Dr. Detwiler.

DR. DETWILER: It might not be so hard to get a handle on it, as well, because even the gelatin coming in under the exclusion in our regulations does have to come in under permit with the country source, as well as the species source on it.

Those facilities are checked by our inspectors, as well, to make sure that there is no exposure to ruminants. So, I mean, there are other options.

CHAIRMAN BROWN: Is it fair to say that there are maybe three possibilities for the source of gelatin in this country?

We have products in this country manufactured from gelatin that is produced in this country from animals that are raised in this country. That's one source.

We have products made from gelatin produced in this country that is derived from material, bones or skin imported from other countries.

We also have products distributed in this country made from gelatin, which is imported as gelatin. Is that also a viable source or has that not occurred? Do you ever import gelatin from other countries and distribute it here?

DR. DUNN: Yes, we do.

CHAIRMAN BROWN: Yes, we do.

And finally, we import products containing gelatin over which we have absolutely no control because they're made in foreign countries.

So four different possibilities for exposure to whatever, and in consideration a little later of sourcing, we probably should address all four.

Well, we can't address the fourth. We have no control over that whatsoever.

Are there any other comments with respect to this particular subject? Yes.

MR. MASTON: Again, I'm George Maston, and I'm President of GMIA.

I think there's still some uncertainty about this question of the balance of gelatin, the extent to which the domestic gelatin manufacturers can supply domestic needs of gelatin, whether it's edible or pharmaceutical.

We've submitted numbers to FDA back in '94 and again in '96 and more recently updated those to show that there is a significant imbalance in terms of pharmaceutical gelatin availability produced domestically in the United States, and that that needs to be supplemented by the import of pharmaceutical

gelatin.

There are present in the audience the major capsule manufacturers, and we do import several thousand tons of pharmaceutical gelatin, a significant part of which is Type B bone gelatin, and of that, as Dr. Vanderveen corrected this morning, probably close to 2,000 tons of bone gelatin comes in from France.

Again, there is a need for it. There's simply not a sufficiency of domestic gelatins to cope with that demand, and I just wanted to make that point clear.

CHAIRMAN BROWN: These are, as you all appreciate getting into questions which are not, properly speaking, scientific, but which are extremely important, namely, we can do all of the science that we want, but unless in addition to that we consider all possibilities of, shall we say, nonscientific things, such as sources, such as regulations, such as this balance, such as our ability to persuade the public that what has been set up as desirable is, in fact, being carried out, this can become very dicey, but I think legitimate questions to discuss.

I think that unless there are further comments about this particular -- yes, at the end of the table.

MR. FAITEK: Doctor, are we discussing the first issue?

CHAIRMAN BROWN: Not yet, not yet.

MR. FAITEK: Okay.

CHAIRMAN BROWN: This is simply the trailing discussion of the open public discussion.

Dr. Roos.

DR. ROOS: Yes, just a comment about the last speaker. Maybe I misunderstood. What I thought I heard was that a lot of pharmaceutical derived material comes from France, and that was pig derived or --

CHAIRMAN BROWN: Type B.

DR. ROOS: Which is?

CHAIRMAN BROWN: I think it's bone.

DR. ROOS: Bone, okay.

MR. MASTON: There are several different types of gelatins coming in from Europe, whether pig skin or Type B bone or hide, but predominantly the material is which is used for hard and soft capsule manufacture in the states which is imported is Type B bone gelatin.

CHAIRMAN BROWN: Anticipating the subsequent discussion on processing because I mention these things as I think of them; otherwise I forget

them. The question will certainly arise later in the morning based on the fact that we know from abundant experience that a high pH, that is to say, a liming type pH is vastly more effective than an acidic pH in the inactivation of the agents under discussion.

Is it a practical matter to consider, for the industry to consider liming skin as well, even though this is not necessary?

MR. WISEMAN: Pig skin or --

CHAIRMAN BROWN: Any skin.

MR. WISEMAN: Well, in the Type B, hide is highly limed.

CHAIRMAN BROWN: It is. So hide is dealt with like bones.

MR. WISEMAN: Yes, exactly.

CHAIRMAN BROWN: Okay. Then pig skin is the question.

MR. WISEMAN: In pig skin, the collagen is much more labile, and if you treat it with any strong alkali, it actually totally hydrolyses the collagen so that it will not form gelatin any longer.

CHAIRMAN BROWN: Even for a shorter period of time, for example, an hour or five hours or a day?

MR. WISEMAN: We have no information on that.

CHAIRMAN BROWN: But it's a possibility.

MR. WISEMAN: It's a thought.

CHAIRMAN BROWN: I mean if we were talking about adding steps that might totally insure the sterility of the final product, that is a step that hasn't been tested, but might possibly be useful.

MR. WISEMAN: Theoretically, yes.

CHAIRMAN BROWN: Yes?

DR. SCHONBERGER: I think we heard initially that there was also some Type A gelatin imported from France, and I don't think we heard what that would -- is that also used for the pharmaceutical? It's a very small proportion apparently, but I would think it's probably --

MR. WISEMAN: If it's pig skin, Type A is normally --

DR. SCHONBERGER: No, no, I mean even from cows, some Type A even from cattle derived.

CHAIRMAN BROWN: I think somebody from the European group, perhaps Reinhard (phonetic) could.

MR. MASTON: Yes, indeed, there is some Type A acid bone gelatin imported, not from France, but rather from Belgium.

DR. SCHONBERGER: From Belgium?

MR. MASTON: Yes.

DR. SCHONBERGER: And is that used in the pharmaceutical industry?

MR. MASTON: It is used in soft capsule manufacture.

CHAIRMAN BROWN: Dr. Rohwer, you had a question?

DR. ROHWER: I had a comment.

CHAIRMAN BROWN: Okay.

DR. ROHWER: I wanted to revisit what Linda Detwiler had to say, and it struck me last night that it seemed to me that really the way this is being regulated now is through APHIS restrictions, and I wonder if the issue isn't whether -- I mean that's the only source of control over the import of gelatin at the moment. At least that's what I'm taking home from what I've heard at the FDA.

And I guess the question is: is it appropriate to have the USDA regulating a material for animals certainly, but for public health? That's really an issue for public health, not animal health, at least as it's being considered here.

DR. DETWILER: May I answer that?

It was looked at. USDA has given authority, you know, by acts by Congress, and our authority extends to animal health, the Animal and

Plant Health Inspection Service. So that's how the exemption got into the rule to begin with.

So you'd have to go back actually to Congress to get that changed, and I'm not being a bureaucrat. That's reality.

DR. ROHWER: No, I'm not proposing that you change it. All I'm saying is it seems to me that the FDA, who I would gather has responsibility for -- well, maybe I don't understand what you're saying. You're saying that the USDA has responsibility for food safety as opposed to the FDA. Is that what you're saying?

DR. DETWILER: No. I'm saying that our authority extends to animal health. If we can even show the slightest link, the possibility of going into the animal health --

DR. ROHWER: Oh, right. I don't dispute that, but what I'm saying is: is the issue before us right now that there's also an issue of human health involved with the gelatin issue? And so the question is: is it appropriate then for the FDA to rely on APHIS and APHIS restrictions for the purposes of animal health to protect human health?

CHAIRMAN BROWN: Response? Oh, you don't want to respond or can't.

DR. DETWILER: I think Dr. Vanderveen said that --

DR. ROHWER: That's a question for the FDA, not to Linda Detwiler.

CHAIRMAN BROWN: Right, okay, fine.

Just a second, Dr. Schrieber.

Have we got a response from, yes, the FDA?

DR. VANDERVEEN: Maybe I didn't make myself clear. Let's say that up to this point in time gelatin is considered by the Food and Drug Administration as generally recognized as safe. The law, the food additive law which was passed by the Congress in 1957, said that all items that were in the food supply prior to that time are considered GRAS, unless, of course, the agency finds that there is a problem.

The purpose of the meeting today is to address whether gelatin should continue to be considered safe under all conditions. If we find that there is some reason to change our position relative to the safety of gelatin, we can do it. It would mean that we would have to promulgate and change in some way or some form the regulation of gelatin to make sure that it continues to be safe.

We will do so if it's necessary. We

always have inspected gelatin producing plants to make sure that there is proper sanitation and things of that sort, but we have up to this point in time considered gelatin to be generally recognized as safe, and the acronym GRAS is applied to it.

Is there a question on that? Okay. Thank you.

CHAIRMAN BROWN: So to rephrase what we've just heard, because gelatin is presently considered to be safe, all regulation regarding it since it is an animal product originates from the Department of Agriculture. If it should prove after this meeting or at some time in the future that gelatin is considered not necessarily safe, the FDA would generate appropriate mechanisms to address that issue of safety.

Is that proper to say that?

DR. HELLMAN: Dr. Hellman, FDA.

Perhaps I can just summarize and clarify. What Dr. Vanderveen said earlier, what Dr. Chiu said earlier, absolutely correct.

The issue before us today is to assess the safety of both imported and domestic gelatin for use in products administered to humans, whether they are foods, whether they are drugs, whether they are

biologics, whether they are devices.

The Department of Agriculture is responsible for animal health. We're responsible for human health. We have the wherewithal to use whatever means we feel that are necessary under our regulations to address the issue of gelatin, and we can take appropriate action.

The regulatory authorities that the different centers operate under are somewhat different, but there is the wherewithal to address that if the Committee decides that there is something further that we need to do with regard to gelatin safety.

Does that put the subject at rest?

CHAIRMAN BROWN: Yes, thank you very much, Dr. Hellman. It's good to rephrase the issue before the Committee from time to time which we can forget.

Yes.

DR. DETWILER: Dr. Brown, before it gets into looking like USDA and FDA were so off in different directions, that's really not the case because if you look back at what Dr. Gray said yesterday, when we first put our regulations into place, is that there was so little known, period, about transmission and about the products with BSE.

It was so new a disease that we considered, even though at that time everyone thought that with the problem would be with the species, with no species barrier, and that's why our regulations with little information went into place right away.

And we were actually considering relaxing our regulations in step with OIE and WHO in the recent years until last year. So with some more information now because there wasn't this thought of the possibility of a human health connection.

CHAIRMAN BROWN: Dr. Honstead.

DR. HONSTEAD: John Honstead for FDA.

Having worked for both agencies, even though they're two separate agencies I want to emphasize, and it hasn't been mentioned yet, that there's a tremendous amount of cooperation and communication between these two agencies, and especially when public health and animal issues are the subject, and there are many precedents for USDA regulating human health.

Trichinosis in pigs doesn't make the pig sick, but it makes people very sick, and APHIS has regulations to keep trichinosis out of pigs, and many of the regulations in the slaughter plants are to keep the meat clean and healthy for people.

So these are two separate agencies, but we work together an awful lot, and we share regulations, and because we communicate we're able to accomplish for both animal health and public health.

CHAIRMAN BROWN: Yes, Dr. Schonberger.

DR. SCHONBERGER: For me the careful selection and sourcing is the nuts and bolts of assuring the safety of the gelatin rather than relying totally on the inactivation.

We just heard somebody say that if we were to source by, say, country or something and say, well, France is a BSE country and, therefore, not want that as a source, that we might get into some shortage problems. Is that what I was kind of hearing?

I was wondering if there are ideas on the table that people could put for how to sourced other than saying a whole country. Is it practical to divide that up into smaller units, even like herd or district?

I know, for example, in the United States if we had BSE I wouldn't want the whole country to be labeled a BSE country, but probably maybe a state or county or something of that sort. I was wondering if that's appropriate to discuss.

CHAIRMAN BROWN: I think that that is

appropriate to discuss, but let us defer it for the discussion of sourcing, which we are not in principle doing right now, although this is happening.

What we actually have is an open public hearing, and it's turned out that most of the folks who are talking now are not, shall we say, in the open public. Are there any further comments, questions from the floor?

Dr. Schrieber. We can always count on Dr. Schrieber.

(Laughter.)

DR. SCHRIEBER: I'd just like to make a further comment to your request that a pig skin could be treated on an alkaline way. This is not possible. The fact is that the pig skin contains about 25 percent fat and only 15 to 18 percent protein. So the treatment with alkaline with this type of romatiel (phonetic) would immediately destroy the whole product. We would make soap instead of generating fat. The gelatin would stay turbid. You couldn't eat it anymore because the odor and the smell would become horrible.

So it is only a theory. In practice it would not work. You could use the alkaline process only with romatiels which are fat free, like the

degreased bones, like the hide splits. They don't have any fat content any longer when it comes to the gelatin plant.

CHAIRMAN BROWN: Can't you degrease skin?

DR. SCHRIEBER: It's inside the whole structure of the skin. You can't separate it.

Thank you.

CHAIRMAN BROWN: We will now proceed to the presentation of Dr. Rohwer, and, Dr. Rohwer, the title I have is "Existing Research on Processing and Validation of Removal of Infectious Agents." Are you going to cover the field or are you going to limit it to the transmissible spongiform encephalopathies?

DR. ROHWER: Well, first let me apologize for the delay in getting here. I can't always predict what's going to happen on my commute.

And I didn't select that title. What I'm going to talk about is generally some general considerations involved n risk management of these diseases in the context of manufacturing products from possibly exposed animals, and I will try to, where possible, direct attention to the issues that are directly relevant to what we've been talking about.

And so I'll talk with some general slides that I use to address this issue, and then I have a

series of overheads where I just go through the process as it's been described in the literature by Mr. Schrieber in the past and just want to point out a few things that I think we should all be thinking about.

Could we have the first slide? Oh, it's here. I see. Okay.

Well, the significance of risk associated with these agents depends quite a bit on end use, and we've heard a lot of examples here, and it's been a little bit frustrating to me that we've spent so much time talking about food and even emulsions, which would be at best an incidental exposure to the BSE agent, and I don't believe that anyone feels that there's any risk associated with these types of exposures.

We know, for example, that the British have been slaughtering animals like this for a decade now, and there hasn't been any epidemiological correlation with the slaughterhouse and people who get a lot of exposure basically, incidental exposure.

Cosmetics would be topical, I guess, and food is the oral route, and a lot of the uses of gelatin that we've been discussing are really equivalent to food type exposures because they are

oral.

In my own mind, the riskiest use is in parenterals, and that seems to be a much more limited use and from a very much more limited source, though I must say that I'm still not clear after everything we've heard here about how much of the parenterally used gelatin actually comes from bovine sources and bovine bone sources, in particular, bovine source gelatin being the riskiest of this family of materials.

Well, this is just an elaboration on that. Certainly in terms of we're much less risk tolerant of luxury, nonessential types of uses for a product than we are for things that we view as essential and critical, for example, drugs which actually have nonbenefit, and we're also -- sorry -- and we're also much more tolerant of traditional historical uses of products, and here food is a good example.

We really depend on the consumer a lot for the safety of food. We have to cook it before we eat it, things like that. It takes a lot of responsibility. Most people are trained throughout their life to throw away meat after it's been in the refrigerator for more than a week or so.

And also the size of the population that

might be affected is a factor. Factors affecting transmissibility, the titer in the source tissue, it varies probably a great deal between hide and bone that's been exposed to central nervous system tissues via the skull or the spine where that remains an issue, and even that is a little bit unclear.

The stage of the disease, the infectivity in these animals increases, well, where we know something about it, which is the rodent models of scrapie. The infectivity increases from the time of inoculation to the time of clinical disease and death of the animal from the agent, and it generally increases in an exponential fashion, which means that if you take an animal very soon after it's been inoculated or very early in the disease, it probably does have very much lower titers than an animal at the clinical stage.

And it's important to note here that most of our steers and heifers, at least, are slaughtered before they're 18 months of age for a disease which has an incubation time of more like four years. So they are probably very early stage.

Route. The efficiency can vary a great deal between the intracerebral and other routes. A hundred thousand-fold is the estimate for the

difference between a direct brain inoculation and an oral feeding type of exposure for most TSE agents, the experimental TSE agents. These are mouse adapted, hamster adapted scrapie strains large.

BSE may be different, and I think that's been alluded to several times here. It doesn't fall perfectly in step with the rest of the spongiform agents with respect to some of these issues. It has clearly been transmitted by the oral route in the case of the BSE epidemic in Britain. It has moved to more than one species, not just to cows, but also to cats at least and several antelope species. There may be something peculiar about it.

Host barrier. The host barrier effect is only in place in the primary transmission. By the time you get to the secondary transmissions, it's gone through some sort of adaptation, and there are several factors that can affect this host barrier effect and host susceptibility, but probably the most important one is the PrP gene itself.

This gives you an example from mouse adapted scrapie of how the infection efficiency can vary with route of exposure, and the way to interpret this is that an IV exposure, to get infection by the IV route, requires ten times as much agent as to get

an infection by the IC route, and IP route ten to 1,000 times as much, subcu. 1,000 to 10,000-fold.

And the oral route. In those instances in which it has been examined, and that is very limited, is much less efficient than the IC route. It is, however, presumed to be the natural route in sheep and BSE and FSE must have been oral. Kuru, it was transmitted by cannibalism among the Fore. It may have been an oral exposure; it may have had something to do with preparing the food for consumption. That's not clear.

The point I'm making there where it says processing may increase the size of the contaminated lot, that's possibly relevant for the gelatin issue. If you take a cow and cut it up and cook T-bone steaks from the transverse sections of the spinal column, you're only exposing a few people in that process, the people that eat that particular cow.

On the other hand, if you take the bones of that cow and mix it with 10,000 other cows and make gelatin from it, if there is an infection associated with that, you've now spread that to the whole lot, and there's a larger exposure, population exposure, as a consequence of that, potential exposure.

Topical, that's obvious.

Parenterals. I don't want to make those points here.

Sourcing. We've had a lot of discussion just in the last few moments about sourcing. This is an excellent way to go about it if you're absolutely confident that you've got a source that has not been exposed to BSE and could not have BSE.

Most of the things on this slide, however, are irrelevant because closed herds are really not a possibility for something like gelatin because there aren't any closed herds that big and aren't likely to be.

Agent specific means that by sourcing to satisfy one criteria, you may be exposing yourself to some other hazard which you have to consider.

And finally, foreign sourcing. What's being referred to there is that a lot of manufacturers of biologicals and pharmaceuticals are turning to Australia and New Zealand for the sourcing of their raw materials simply because these countries do not have endemic scrapie and are considered to be very low risk for these diseases.

This is a review of countries which have had BSE in the past. We've been over that in this meeting several times. So I don't think we need to

belabor that.

Risk issues for sourcing. I think it's worthwhile going over this. The countries which are relevant to this discussion are probably the United States, Europe, Australia, and New Zealand. The great advantage of Australia and New Zealand is they have no endemic scrapie, and if scrapie is a risk factor for BSE, then these are probably the most secure places we can go.

On the other hand, they do feed meat and bone meal there. They do still render, though it's under review in both countries, and it's being curtailed, or so I've heard recently.

In the United States, we have excellent surveillance from our point of view, though it is questioned by EC countries often for marketing reasons as opposed to safety reasons, I have a feeling.

In Europe, the surveillance is questionable, is highly variable, and I think Will Hueston made that point yesterday, and it's been questioned in the case of Australia and New Zealand.

Certainly they have very good quarantine practices and that sort of thing, but how well they actually, especially in Australia where they have vast commercial flocks, how well those are monitored is not

clear.

Feeding of meat and bone meal, sheep scrapie, imported cattle. All of these countries have been exposed to, potentially exposed to BSE through the import of cattle from Britain before we became aware of BSE. There have been trace-back efforts in all these countries. Most of these cattle have been found. However, some of these animals were rendered.

And just by way of stating that this can be a risk factor, a cow like this in Alberta a couple of years ago did come down with BSE, and so it can happen, and it is a potential source of exposure, and it's a potential source of introduction of this agent into the rendering stream.

In our country, we have a couple of potential reservoirs for these diseases. We have chronic wasting disease of deer and elk, and our expert on that has left it looks like, and then we have these outbreaks, sporadic outbreaks of transmissible mink encephalopathy for which some of which appear to be related to cattle exposures.

There's good news and bad news in that. The good news is that these things happen very rarely. So if the mink is a sentinel for this type, for something else that's circulating in the cattle

population, it's something that doesn't happen very often.

The bad news is there might be something there.

I'll skip that for now.

The prion hypothesis in sourcing. Implicitly in the prion hypothesis is the idea that you could have spontaneous generation of these diseases, and this is something that is seriously proposed by people espousing this model. The idea is that the disease is simply caused by this protein which is found in all mammals, and a transformation of this protein from one form to another, from its native form to an amyloidotic form is the process by which the infection occurs.

If you take this amyloidotic form and inoculate it into another animal, you can propagate it because it recruits the native form into the amyloidotic form, and the infection progresses.

This is a purely chemical model of the disease based on an endogenous protein, and the feeling is that there's some potential energy barrier between these two forms, and there must be spontaneous transformations from one form to another that occur from time to time, and if such a thing happens, it

would be a way of initiating a new instance of spongiform encephalopathy in that animal.

Any animal for which it can be demonstrated experimentally that they are susceptible to spongiform encephalopathy would, therefore, be at risk for these diseases.

What this means is that there's no way, if this hypothesis is correct and if this model is correct, there's no way to eliminate exposure to this disease. It's always going to be there. The question is: is there any way to prevent it from expanding?

And the lesson we have learned, I think, in spates from the BSE epidemic is, yes, there is if you prevent the intraspecific recycling of foodstuffs and biologicals within the species. You can break the cycle, and that's because in most instances the TSE diseases appear to be dead end diseases. That certainly seems to be true in humans, and in the case of sporadic disease, and it looks like it may be true for BSE in cattle as well.

The epidemic is falling off very dramatically in response to the food ban instituted some years ago, and it remains yet to be seen whether there'll be a reservoir of endemic infection once this huge background has flushed out of the system. The

British epidemiologists at least feel that there will not be.

So what this means is that when the disease arises like this, we might never see it, especially if it was in a young animal, unless that animal is recycled. So there's a route of transmission from animal to animal.

We've been over this issue, and the only points I wanted to make here is the WHO and European Union have categorized the tissues from animals into these risk groups based on the experimental data, such as it exists, implicating their relative infectivity levels, and Dr. Wolfe mentioned yesterday some of the caveats associated with these classification systems, and I just wanted to reiterate them here.

Many of these assignments are based on a very few, one or a few determinations. Often the volumes that were tested were extremely small. They were tested across a host barrier, which means its sensitivity was low, and at best, the sensitivity is less than 100 LD50 for that Class 4 group.

Slaughter is another issue. Slaughter is a highly regulated process, but the regulations are directed at food safety, not biological and pharmaceutical safety.

To the extent that gelatin is used and we are exposed by oral routes, that's appropriate. To the extent that it's used for parenteral purposes, perhaps it's not, and there are some vulnerabilities, a number of them.

There are the possibilities for same species contaminations between animals. In the process of slaughter, the order in which things are done in the United States anyway, typically the animal is killed, it's bled, it's delimbed, decapitated. Actually it's skinned before it's decapitated, eviscerated, split, washed and chilled, and in the kill step there's a point of vulnerability there because the captive bolt penetrates the skull often, and CNS material, central nervous system, brain material leaches out of that hole or oozes out of that hole.

At the point of decapitation, you're actually separating the head from the spine. It's important to note that the infectivity titers in spinal cord are equivalent to those in brain, and the splitting step is probably one of the most grotesque from the standpoint of contamination because the saw goes right down the spinal column.

The solutions. In the case of gelatin

manufacture, I don't think there are any. There could be because they need to draw their raw materials from such a vast source and the scale of gelatin production is so enormous. It would be impossible for them to control it any more than it is being controlled at the time of slaughter.

On the other hand, in Britain, for example, my understanding is that they now take out the spinal column without splitting down the center, and you know, if that kind of practice comes into general use, it may offer some additional safety, provided that there's not some exposure at some other step to this material.

We went over this slide yesterday, and the main point I want to make here is that in the processing of gelatin, there are lots of other steps, and we'll go over that in more detail in a minute, that may offer possibilities for removal.

On the other hand, these separation methods don't actually kill the agent, and as a consequence, if there is infectivity present, it's still there, and that needs to be recognized and appropriate measures need to be taken to deal with it.

The most important danger probably is cross-contamination from the waste stream in a plant

like that back to the product.

Aggregation, again, is dangerous if it's unrecognized in a validation study because you may think that you've removed something and you haven't.

Facilities contamination. Well, people who make pharmaceuticals and biologicals go to great pains and have to satisfy very explicit regulations on how to isolate one batch of their product from the next and how to prevent cross-contamination of the product from the raw materials. This is not so important or so rigorously -- not rigorously enforced, but rigorously regulated in these raw materials types of industries, but here are some of the points that should be considered.

The risk is greater when the removal steps don't kill. That means the stuff is still there and offers a potential for cross-contamination.

The TSE agents, the reason they are so difficult to deal with, one of the reasons, is that they do persist indefinitely in the environment. There are lots of anecdotal tales of people scraping the infectivity off of path. slides that are 50 years old and inoculating it into animals and discovering that the stuff is still there. It seems to survive indefinitely on fomites.

Ways to get around this are to use barriers and flow control to isolate the product from the removal steps, and of course, in most instances you can employ much harsher treatments in sterilizing equipment and facilities than you can for sterilizing product. So it's not unreasonable there to use high temperature steam for long periods of time and to expose things to harsh reagents like sodium hydroxide and bleach, especially in a stainless steel environment.

Batch size. I believe this is self-evident, but the larger the batch, the greater the risk, and the reason here, of course, is that if you have a contaminated animal and it ends up in a batch or if contaminated animals are in the picture and they're there at, say, one in 1,000 and you have a batch size of 100, you have a smaller probability of contaminating that batch than a batch of 100,000 or a batch of 10,000.

We had a very tragic lesson in batch size in the story of cadaveric human growth hormone, where the manufacturing batch sizes were about 10,000 pituitaries per batch, and retrospectively that meant that practically every batch was probably exposed.

Now, I want to make one more point, and

that's a point about dilution. The batch size has been used as an argument in favor of elimination of the agents, and the argument goes this way.

Well, if the titer required for infection is one infectious dose and, say, we have 100 infectious doses and the batch size is such that it's going to be distributed to a million people, then the dose per person is going to be extremely small, and as a consequence, there's really nothing to worry about.

In the case of these agents, and especially -- this is a fallacious argument in my mind -- and the reason for that is that the infectivity does survive dilution, and by way of showing you why I'm confident that this is true, I've just given you an example of what happens in an endpoint dilution titration.

If you inoculate an animal with ten infectious units, indicated by the little circles there on that hamster -- and forget the text here because this was designed to make a different argument, but it makes the point nevertheless if you forget the text and we just look at the diagram -- an animal that gets ten doses is clearly going to come down with the infection. If you dilute it tenfold, on average all the animals will become infected.

Actually it'll be distributed by the Poisson. So about 37 percent of them will.

You dilute it another tenfold, and approximately one in 100 will become infected, and you dilute it another thousand-fold, and one in 1,000 will become infected. You can do this indefinitely down to your very, very small dose size.

And the point of this is simply to say that in the case of these agents, they won't go away with dose, and as a consequence, what we should be considering is not the exposure per dose, but the exposure of the population when we talk about this stuff.

So, for example, if you end up with a batch of gelatin and you know that from your risk calculation that there could be ten infectious units associated with it, those ten infectious units and the whole thing will be consumed by people eventually; those ten infectious units will go into ten people somewhere along the line. The risk per person may be extremely small, but it will all get out there.

Now I want to say a few things about validation because that was another big point of discussion, and there are lots of problems with validation of these animals, a lot of caveats

associated with validation. I think it's important for people to be aware of what those are. Nevertheless, I don't think there's any questions about the value of validation in terms of adding extra assurance to the security of products exposed to these agents.

Nevertheless, any one experiment or relying entirely on validation is probably not a good idea.

There are three major components to this process: one, selecting an appropriate animal model, an appropriate challenge once you've selected the animal model in terms of what you're going to actually put in your production stream or what you're going to actually try to inactivate; the context of the infectivity; the endpoint and the spike. We'll go over those one at a time here.

The issues involved with animal models are relevance. We discussed that a little bit yesterday in response to a question from Dr. Roos. It is an issue. There are lots of possibilities.

The laboratory strains, the useful ones, are in mice and hamsters, and they are either Creutzfeldt-Jakob disease adapted to mice or scrapie adapted to mice. There is a BSE strain that's been

adapted to mice, but as far as I know, no one has used it in a validation to date.

In terms of relevance, it's important to consider the following. There are differences in the host animal from which these diseases are derived. We have BSE. We have scrapie. We have Creutzfeldt-Jakob disease. At least within the spectrum of scrapie and Creutzfeldt-Jakob disease there are a number of different animal isolets that have been derived from field examples of both of those diseases, and they differ quite a bit in the mouse adapted form from one another.

So it's not even clear at the animal level or at the disease agent level which agent to pick. Do we work with 22A, ME7, 263K, et cetera, if we're dealing with a scrapie model, or in the case of Creutzfeldt-Jakob disease, there are a number of different strains of Creutzfeldt that have been isolated, as well?

Are these strain differences any greater within an agent class, any greater than the difference between the agents themselves? That certainly is not clear to me.

Titer is an important issue. The reason we favor the hamster model or I favor the hamster

model, anyway, is we have 100 times more infectivity to work with than we do in any of the mouse models. This offers a lot of advantages. We can dilute the agent more into the vehicle so that we don't have as big an impact of the spike on the process. It also allows us to demonstrate higher levels of clearance where that's expected.

The time of incubation is also important. In the hamster model, an experiment is over pretty much in six months, certainly by a year; whereas a mouse takes a year to 18 months to complete.

There's a biohazard issue. Most of us would prefer to work with scrapie if we could compared to Creutzfeldt-Jakob disease, and when it comes to BSE, my understanding is the issue of whether or not we could use BSE mouse for validation studies in this country is still under review by the USDA, though it might be worthwhile.

Availability, that really has to with chimpanzee studies and CJD and expenses. All of these things are expensive. It gets especially expensive when you're doing monkeys.

The challenge. It's pretty clear what the appropriate challenge is in the case of the gelatin story. We're worried in this case about central

nervous system tissue contamination of bones that are used to obtain gelatin.

It's less clear for something like hide. I would expect that hide has no indigenous infectivity or intrinsic infectivity, and if there is infectivity associated with hide, I would expect it to come from the same source.

Certainly the difference in titer between central nervous system tissue and hide, for example, must be at the level of ten to the fifth or ten to the sixth, and it's much more likely that you have an adventitious contamination than something that's intrinsic.

On the other hand, if you have intrinsic infectivity in a tissue, then you always have to deal with the issue of is it valid to add it, add infectivity extraneously as a test of whether or not you can remove that infectivity. This would be especially problematical for a solid tissue like hide. How would you introduce this stuff in a credible way to show that you had gotten rid of it in a credible way?

Strain of infectivity, we just talked about that. Then how do you introduce the spike? In the case of gelatin in the experiment discussed by Mr.

Schrieber, brain homogenate is probably perfectly reasonable because that's probably the nature of the contamination.

In other tissues it may be less so, and so there are these other options that one can use for the form that the spike takes.

There is one point, however, that I think we do have to consider, and that is the test that was done was done on a brain homogenate, whereas the actual process is conducted on chunks of bone or hide that are exposed to these agents, and with the encouragement of the result that the industry has obtained so far, it would be nice to see them to make an attempt at least to create a more realistic challenge in terms of the form in which the tissue is presented to the lime and the acid.

Actually I think I just covered those issues.

Finally, because there are so many variables in this process, the choice of the agent, the choice of the strain of agent, the nature of the spike, the context of the spike, that sort of thing, and because it's often impossible to do the experiment on the system we're actually interested in, i.e., BSE in cows or CJD in humans, for example, the way to gain

the greatest amount of security from this type of investigation is to do it in several different ways and hope that the results of these experiments all converge on the same answer, and that gives one the confidence to extrapolate the result to the real world.

Now, if we could just go over very quickly, I made some overheads in which we could consider some of these points in the context of the bone gelatin production. Let's put that on at the end. That was an -- just hold that one, John, and start with the next one.

This is an overview of the bone gelatin manufacturing process, and I took this from the published account of this process by Schrieber. It was published several years ago, and what I'm going to do is just go through this process and highlight some of these steps and make a few points about them.

Next. I'm going to challenge your dexterity here.

Sourcing. The issues involved here are the U.K. risk factors versus the European risk factors versus the U.S. risk factors, and we made the point already that the volumes required are too large for closed herd solutions, but we are getting gelatin

apparently from the U.K. and from Europe, and the question is: are these three sources equivalent? And it seems to me that that's one of the questions or that's an element of one of the questions before us. It's not clear to me.

Inspection. It's important to note that all of these animals that are inspected, they're all food grade animals, but these inspections, there is no way to detect pre-clinical cases of these diseases.

The slaughter step, there is a lot of CNS or there is potential CNS exposure at the kill stage, at the decapitation, the split, and the mechanical -- split stage and possibly at the stage of mechanical recovery of meat. It sounds to me like they're using these hydraulic methods on some of this material before it ends up in the gelatin process.

And of course, the big issue is how much of the CNS exposed bone material actually gets into the gelatin manufacturer, and we've heard that an attempt at least is made to remove heads and keep them out of the process, and that, of course, is encouraging -- next -- though it sounds like it's quite possibly imperfect.

Batching. My understanding is that the exposure in terms of cattle number per batch in these

processes is from 2,000 to 10,000 cattle per batch, and that by the time the gelatin is blended, the exposure per batch could go from 10,000 to a million cattle.

Next.

Milling. I think one of the major vulnerabilities of the validation test that's been conducted by the gelatin industry to date is that it was done on brain homogenate, whereas the actual process is on these chunks of tissue of 12 millimeters in size.

And as I tried to point out yesterday, this could be important because if these agents can find a sanctuary from the inactivant, they may not be inactivated, and with the process in such an inhomogeneous state at the steps at which the inactivation occurs, there's the potential for this, and it would be very reassuring to see this redone in some way to address this issue.

I can think of some possibilities. For example, you could take the spinal column of infected hamsters and challenge, break that up into pieces and challenge that with the liming step, acid liming step, and see if that works.

The washing and degreasing steps.

Certainly this could be very effective in removing superficial contamination from these agents and dropping the titer very significantly. It would be very hard probably to do this in a scale-down, but it might be worth attempting.

Again, it's removal. It's not inactivating, and there's this issue of what becomes of the washes from this process, and there's the potential, of course, that these washes could expose the product in the plant to these agents if they are contaminated.

The drying step. There's a possibility that it could also offer some inactivation of these agents. It's at 100 degrees, and there are a number of reports in the literature that 100 degree exposures can result in a couple logs of inactivation, but it would definitely require validation.

Next.

Demineralization. One normal HCl has been looked at a couple of times, and on the scale of one hour it's been very ineffective, and in general these agents are insensitive to acid, but these long exposures have not been tested before, and it's of interest to me at least that it looks like it does something when you drag it out for days and days.

The alkaline digestion is, of course, the most important -- has the best prospects for inactivating these agents, but the concentration that's used has been shown to be borderline efficacious in experimental systems, but again, these long, long exposures have never been tested, and it looks like it may offer quite a bit of inactivation.

Next.

Filtration. Any process that involves a lot of surface area tends to remove these agents. At least that has been my experience, and so filtration, even though it's not nano filtration, even though it's filter presses and diatomaceous earth, does offer definite prospects for significant removal of infectivity from this material.

It's very hard to scale down these filtration steps in a credible way, but when it has been done, they tend to remove several logs.

Of course, it's not inactivating, and then you have to consider the fate of the filter and how the filter press is sterilized between batches.

Ion exchange, the same thing. I'm not at all convinced that the removal is based on ion exchange, but nevertheless, this stuff seems to stick to the plastics, both cation and anion exchange

columns, and just exposing it to those steps is liable to have removal potential.

And finally, the sterilizing and drying step. This is the most intriguing to me because the temperatures are adequate. The time of exposure that's in the published account, four seconds, is far shorter than anything we've been able to do, but it would be nice to try to scale this down and actually try to validate this process.

It does need to be validated, however, and I don't think that the published work from myself should be relied on as a source of inactivation from this process.

The other thing I want to say about it is this drying and sterilization step, I believe -- I'm still not clear about the details of these things -- occurs at atmospheric pressure, which is quite a different situation than placing the material under an atmosphere or more of pressure at these same temperatures.

And I just wanted to say something about hide gelatin. Hide offers a lot more security simply because it's removed early in the slaughter. It can be protected from the central nervous system during the slaughter process quite well, and it shouldn't

contain any intrinsic infectivity, and the .3 normal sodium hydroxide is a much more stringent exposure than the lining process, and in our hands, even an hour or less exposure to those concentrations should remove five or six logs of infectivity.

Next. Can we have the last one then?

And then I just wanted to put this one down. It seems to me that the discussion here has been very confused in terms of the end use, and from my point of view anyway is the most important consideration, and exposure by the oral route, whether it's as food or as capsules, seems to me to be equivalent.

These are animals which are being eaten. We're producing gelatin from a component of these animals and then eating that. How can this be any different than the exposure we're getting from food, except possibly this batch argument, that by batching it in very large batches we might be exposing more people to a given infected animal than we would through the supermarket, for example?

On the other hand, parenteral routes offer much higher risks, and I would like to know a lot more about those applications, and it seems to me that's where we need the greatest level of assurance that

we're not getting exposures.

That's the last slide, except for a table I made out last night which I wanted to put up here. This whole discussion has been -- if nothing else, has illustrated how complex this industry is and how complex this web of interactions between nations and sourcing and production methods and end uses is, and it seems to me before it would be possible to make a really rational decision about how to manage gelatin, we need a lot more information.

And I would love to see a table like this that essentially lays it all out in front of you. The country of origin of the gelatin, now we're talking about U.S., our exposure here in the U.S. to gelatin. The country of origin of gelatin that ends up in the United States; the animals from which that gelatin is derived; the tissue from those animals from which it's derived; the process that's used, and I'm just giving this as an example, and I'm not even sure that's an accurate example, but these are things that were mentioned during the day, and this is the way a table like this could be filled out; those parts of that process that offer removal potential and security; and then the products and the route of exposure that we get from those products.

Now, I think if we had a big, global view of this, it would be a lot easier to make a decision about how to deal with these things. For example, is the same plant that's making emulsion gelatin on Wednesday making from bovine sources -- I don't even know. I guess emulsion gelatin comes from pigs -- but are these plants making one form of gelatin one day and another form on another day? And if so, what are they doing to separate those processes and the exposure that's associated with that?

And how secure are these lines of supply in terms of tracing them back to countries of origin, for example? Those kinds of issues, and I'll stop there.

CHAIRMAN BROWN: Thank you, Dr. Rohwer.

Are there questions for Dr. Rohwer?

DR. ROHWER: Linda.

CHAIRMAN BROWN: Yes, Dr. Riemann.

DR. RIEMANN: Well, it occurs to me that if most of the gelatin manufacturers are on the ISO 9000 standard, all the information you are asking for should be available.

DR. ROHWER: It would be nice to have it compiled. I guess that's what I'm asking.

CHAIRMAN BROWN: Dr. Detwiler.

DR. DETWILER: I had a question, Dr. Rohwer. Spontaneous occurrence, we hear that more and more being thrown up. Now I hear it expanded not only from cattle, now to all the other animal TSEs, as well, and I would ask what other evidence do you have other than the anecdotal TME evidence, as well as in the observation of CJD occurs like this, so the animal TSEs must occur like this?

I mean I hear that more and more, because I would say that epidemiologic evidence with the animal TSEs would argue against this spontaneous occurrence and then transmission, and I'll give two examples, and the first is scrapie.

With scrapie there's a lot of evidence that scrapie is laterally transmitted between unrelated sheep, and then recently in New Zealand especially, they genotype their sheep, and they do have a very large susceptible population, and they have over 100 million sheep. So you would think if it spontaneously occurred and then laterally transmitted, there would be evidence of scrapie there.

So I think New Zealand actually argues against that occurring with sheep scrapie.

My other thing is with the BSE, is TME is not only reported in the United States, and I think

people tend to forget that. TME has also been reported in Finland, Germany, Russia, Canada, in ranch raised mink, as well, back. I mean the last reported case was in 1985 in the United States.

And the fact that these countries also fed this ruminant protein back, yet the occurrence of BSE in the countries of Europe do tend to all be linked back to the U.K., then how would you explain these other TME cases, and why hadn't we seen evidence of BSE with the recycling back in small populations?

DR. ROHWER: Yeah, thanks for bringing that up.

I don't care for this hypothesis at all, and I think you're aware of that, but some of the most prominent figures in this field have promoted it very heavily, and it is in front of us, and it is being considered.

I think the other evidence is our own country. I mean we've been recycling for years and years and years. We have 100 million cattle or thereabouts in this country. We should have 100 cases per year at one per million per year, and there's been no evidence of this occurring here.

The vast commercial sheep flocks in Australia, you could say the same thing about them.

I don't think there is any good evidence for it. It's a hypothetical argument that fits very nicely with the prion hypothesis and the one per million per year instance of Creutzfeldt-Jakob disease, and as I say, it's -- but I think what's important to realize is you can't -- it's important to raise these arguments against it, but you can't ignore this argument because it's out there and it has credibility with a number of people who have a lot of credibility.

CHAIRMAN BROWN: Other questions for Dr. Rohwer?

Dr. Dunn, did you scratch your head or do you have a question?

DR. DUNN: Just scratching.

CHAIRMAN BROWN: Okay.

(Laughter.)

CHAIRMAN BROWN: Yes, Dr. White.

DR. WHITE: Just a question along that same line. Does it matter when cattle are looked at? For example, if you have predominantly a dairy herd that might live longer, you might expect to see more BSE. If you had a primarily beef herd, which would be sacrificed earlier, you might not see it. Does that enter into any of these?

DR. ROHWER: It certainly does.

DR. WHITE: It's like the question that Linda asked.

DR. ROHWER: Yeah, it certainly does. I mean, again, the animals raised for meat get slaughtered at a fairly young age, and you really have no hope of seeing BSE in those animals even if they're incubating it, and that has been a source of criticism for the USDA surveillance in the United States coming from the European countries.

And I guess in that same line, if the British do as they're proposing to do and slaughter all the animals that are older than 30 months, we'll never see another case of BSE in Britain either. It doesn't mean it's not there.

So that is an issue, and it looks to me like Linda might want to make a comment.

DR. DETWILER: Yeah, I just wanted to say with our surveillance we don't look. In fact, we don't look at animals that are under two years of age for that because we could rack up a lot of brains, but that wouldn't be valid data, and I think we're even, you know, saying to labs we don't want the data if it's under two years of age, the labs that feed into our system.

We are going, especially in our random,

systematic slaughter surveillance, we are going to those plants that kill those dairy cows that are older, that are culled older, that are also -- with these downer cows -- we're using both the histopathology, as well as the immunohistochemistry.

Plus the dairy animals would most likely to be fed or have been in the past fed the protein, the meat and bone meal protein. So we're really concentrating a lot of our surveillance on the population that you would think would be most likely to be exposed.

CHAIRMAN BROWN: Dr. Schonberger.

DR. SCHONBERGER: If you were an owner of a gelatin manufacturing company, would the tests that they're doing to validate the inactivation be the one that you would do? And what would be the next? You listed a whole bunch of steps and a whole bunch of things that you might want to do. I'm trying to get you to focus on perhaps the two most important tests that you might recommend for validation of the process as you understand it now.

DR. ROHWER: Sure. In terms of weighting the significance of these steps, inactivation is always more desirable than removal, and they have focused on those steps which offer a potential for

inactivation, and that's appropriate, and the tests that they have done suggest to me, anyway, from the data that's been presented that they're getting some inactivation in those steps, and it's not unreasonable, especially in the liming step, to expect that.

The step that hasn't been directly investigated are the thermal exposures which could also offer inactivation, and I would find it comforting to see inactivation at those steps, as well.

But then there are a number of other steps in this process which at the level of removal, not inactivation, could remove a lot of infectivity, and those are the things that I mentioned. The washing steps, the filtration, and the high surface area steps essentially are other things that I think could probably be looked at.

And the story is that none of those things by themselves are likely to overwhelm you with their significance, but an interesting thing about these agents is that one of the things that has complicated their study is that purification methods don't work very well, and it's because they are not homogeneous. They do stick to everything, and people do suffer

tremendous losses of material when they do things like classical things that you might do with a virus, like chromatography and filtration for separation.

CHAIRMAN BROWN: Are there other questions?

DR. SCHONBERGER: Can I?

Are you saying that there is really nothing that they could do that would totally satisfy you in terms of validation studies that would make you very comfortable?

DR. ROHWER: No, I didn't say that at all.

DR. SCHONBERGER: Okay. So --

DR. ROHWER: I mean, I think they are doing the right things.

DR. SCHONBERGER: They're doing the right things?

DR. ROHWER: Yeah.

DR. SCHONBERGER: So at some point if they were to come out with results on the study that they're doing and maybe the drying study that you're talking about, and it shows inactivation, then you would feel comfortable to call this what, GRAS, or would they call it generally safe for all uses?

DR. ROHWER: There are two parts to a risk management program like this. The validation is just

one part of it. You also have to have some idea of what your exposure is, and that part of the equation still really hasn't been presented here.

It's presumed to be very small because the idea is that you might -- in one of these batches your exposure might be to one animal that's diluted into 10,000 or something. So you have a one animal type of exposure. What could the maximum titer be in that animal, and are these processes adequate to remove that infectivity from that animal? Do we consider things like host, barrier reductions in effective infectivity when we talk about the risk to humans being exposed to the residua.

All those things are factors, and I think it has to be analyzed in a unitary way and presented together before you can feel secure. My guess is that it's probably pretty good, but I'd like to see the whole story in one place.

Do you see what I'm talking about? Yeah.

CHAIRMAN BROWN: Dr. Roos.

DR. ROOS: Maybe just following up on that question, would you be happier if they started with BSE material rather than mouse scrapie in the validation studies?

DR. ROHWER: That would be certainly

interesting. I would -- my feel is that I'm not certain that it's any more relevant than what they've done. It would be interesting because no one has done a validation study on the -- and I'm presuming what you're talking about is mouse adapted BSE, and to do it in cattle, I don't think we want to wait that long. That could be a 15-year experiment.

But there is a mouse adapted strain of BSE, and I think it would be worthwhile to start doing especially comparative studies with that material and see how well or how closely it mimics scrapie in the mouse.

DR. ROOS: Just to push on --

DR. ROHWER: It goes back to my last slide. Where I get assurance, feelings of confidence is when I see it done one way, then done another way, maybe in a couple of different laboratories, and everybody is getting the same result. Then you start feeling like, well, yeah, this is probably the way it is.

DR. ROOS: But just to introduce one other little perspective there, how about BSE material not mouse adapted into a transgenic animal that had a knock-in of either a human PRP or bovine PRP?

DR. ROHWER: I think I would certainly be

highly supportive of experiments like that, but again, I think you'd want them in the context of other experimental work because even those models have not been validated and aren't likely to be for some time.

That requires direct comparisons with cow-to-cow transmissions versus cow-to-transgenic transmissions, and those things are going to take a lot of time just because the whole process occurs much more slowly in cows than it does in mice.

But it would be very comforting to see convergence of all those lines on the same answer.

CHAIRMAN BROWN: If there are no more questions, I would like to remind the Committee of a paradoxical situation with respect to these studies, and that is the last question that we are going to address this morning amongst ourselves is whether or not current scientific evidence justifies the continuing exemption of gelatin from the restrictions recommended by the FDA.

If the Committee decides, and it will be polled on that question, that the answer is yes, it will eliminate all impetus to continue any such studies that have been under discussion, just to remind the Committee that this is an important question to answer.

We will now take a break before we start Committee discussion of the questions that we're asked to answer, and it is now seven minutes past ten.

Dr. Freas, do you have --

DR. FREAS: Could I make a quick announcement?

Because the format of the questions that we are going to be discussing in the next resumed session is a little bit different than the questions passed out in the agenda, I do not have enough copies to go around, but in five minutes the new formatted questions will be posted out in the lobby. Please look at them so there is no confusion over what questions are being discussed when the Committee discussed the questions.

CHAIRMAN BROWN: And the Committee will reconvene at 20 minutes past the hour. That's 15-plus minutes.

(Whereupon, the foregoing matter went off the record at 10:03 a.m., and went back on the record at 10:30 a.m.)

CHAIRMAN BROWN: Thank you for bearing with the slight delay.

Evidently the last comment that I made created some nervousness, and when that happens

lawyers always get involved, and so two of them would like to speak.

(Laughter.)

CHAIRMAN BROWN: One is -- or at least legal counsel -- Dr. Bert Mitchell, the Associate Director for Policy and Regulations of the FDA, and the second is Mr. Safir, General Counsel for the Gelatin Manufacturers.

So in that order, Dr. Mitchell.

DR. MITCHELL: Well, thank you, Mr. Chairman.

I have a great deal of respect for the legal profession. However, I'm not certain of the reciprocity of this respect, and so I would not want to be speaking on behalf of the legal profession here.

I'm a veterinarian and Associate Director of the Center for Veterinary Medicine, and what I thought was important here, and I'll only take a minute to describe this, and that is that the not general recognition of safety, not GRAS determination is made on a use-by-use basis.

So while a lot of the comments up till now have tended to generalize and to discuss gelatin as a commodity, when it comes to the matter of regulating this, it will be regulated on the basis of uses and

Dr. Rohwer's presentation.

So clearly outlining the oral routes of administration, parenteral, food, topical, and incidental, is important in this respect, and I just wanted to be sure that you understood that the not general recognition of safety is on a use-by-use basis.

Thank you.

CHAIRMAN BROWN: Thank you, Dr. Mitchell. Forgive my misappropriation of your professional origins.

(Laughter.)

CHAIRMAN BROWN: Now we will hear from a lawyer. Mr. Safir.

MR. SAFIR: Yes, is this microphone working now?

PARTICIPANT: Yes.

MR. SAFIR: Yes, indeed, I am Special Counsel to the GMIA.

The only short point I wanted to make was that the comment made by the chair at the end to the effect that answering the general Question No. 1 might provide an impetus, at any rate, against the testing or further testing of this, and that to vote in that manner would somehow stop the testing; we would like

to point out that while gelatin has been exempt throughout this period, all the testing that you've seen has been done.

The industry has worked with FDA for the last number of years, fully cooperating with the agency and continues, will continue to do that regardless of how any vote comes out on this. So we just strongly urge you to separate entirely the link between testing, further testimony of the safety of gelatin or further confirmation of the safety of gelatin and any decision you make regarding the exemption of gelatin from the specific restrictions.

Thank you.

PARTICIPANT: What was your name, sir?

MR. SAFIR: Sorry. My name is Peter Safir.

CHAIRMAN BROWN: We now get down to the nets and bolts of this meeting.

DR. HONSTEAD: Paul.

CHAIRMAN BROWN: Yes.

DR. HONSTEAD: I need to --

CHAIRMAN BROWN: Oh, I'm sorry. Yes, I did promise you the opportunity make one comments, which is relevant.

DR. HONSTEAD: In my statement yesterday

about source materials for EC gelatin production, I misstated, and it was later corrected, but I wanted to be sure that it's thoroughly understood.

In the U.K. and France, no heads are permitted to be used in gelatin manufacture. In the other countries of the EC they can be. In the U.K., no spinal columns -- now, that's the bones and the soft tissue and the spinal cord -- in the U.K. that cannot be used for gelatin, and in France the cord must be removed before any food processing is done.

Is that clear? Other countries can use these materials in the EC.

DR. WOLFE: Just a question on that. At what point is the cord removed and how? You don't know?

DR. HONSTEAD: I don't know. It's removed from any potential for human consumption, and I'm not familiar enough with their slaughter process to know where it's removed. I know our process, but that doesn't mean that that's comparative.

CHAIRMAN BROWN: Thank you.

I think it would be useful, Dr. Asher, to provide us with an image of the questions that we are going to answer if you would project them, and I'm going to change the order, but not the numbers of the

consideration.

DR. ASHER: I lined them up three, four, one, two. Is that --

CHAIRMAN BROWN: Yes. That is to say the third, fourth, three, four, two, one actually.

DR. ASHER: Three, four, two, one.

CHAIRMAN BROWN: Well, we can switch back. It's not a major, major problem.

And I'm doing this because I think, first of all, the final question about exemption is properly the final question rather than the first, and I think gelatin processing and validation, the question which is on the screen now, is perhaps the most specific of the questions or the most limited of the questions that we must answer or at least try to, and that is why it is first, and it may also be the easiest question to answer.

And it is as you see: which, if any, specific procedures in gelatin processing is preferred or essential to assure optimal inactivation of any contaminating TSE agent?

DR. WOLFE: Just --

CHAIRMAN BROWN: Yes.

DR. WOLFE: I have a point of clarification here. I assume since we're answering

the now first question last, that the answers to these other questions are independent functions of what the final answer is. For example, whether or not we decide that the exemption should end or continue on this question about which, if any, specific gelatin processing procedures would apply to even the United States, would apply across the board to whatever countries still remain as ones from which gelatin can be imported. Is that correct?

CHAIRMAN BROWN: All but the final question, which involves the exemption, are -- what shall I say? -- non-polling questions. The only question on which the Committee will be polled will be the final one, and so these questions are --

DR. WOLFE: Independent.

CHAIRMAN BROWN: -- independent, and they're really designed to get with very specific focuses the opinions of the Committee.

And so this is a question which the Committee is now addressing. Which, if any, specific processing procedures is preferable or essential to assure optimal inactivation of TSE?

Anybody on the Committee wish to kick off a discussion of this or does anyone have opinions? I suppose we all have opinions. Larry, you half-

heartedly raised your hand. Do you have an opinion?

DR. SCHONBERGER: Well, yeah. I think the alkaline step is a key step, and I'm concerned about the cattle derived material that is with the Type A gelatin because of that. I think we saw that that was the one that they've documented or seem to be showing as perhaps a ten to the three maybe reduction or something of that order, whereas the acid was closer to ten or something to that.

CHAIRMAN BROWN: Yeah, the data isn't in, but it looks --

DR. SCHONBERGER: Yes.

CHAIRMAN BROWN: It should be consistent with what we already know, which is that high pH has been traditionally and regularly more effective than low pH, and therefore, a liming procedure would be expected to be more effective in decontaminating than an acidifying procedure.

DR. SCHONBERGER: Yeah, basically, right.

CHAIRMAN BROWN: Dr. White?

DR. WHITE: It seems to me unless you can show that one step gets rid of essentially all of the material, one has to consider a sequence of steps. I mean, you may be able to rate individual things. I would certainly think that alkali would be important,

but I think temperature is important. I think washing is important. I think all of those steps, if there's no single step that gets rid of the TSE by itself, one almost has to consider the entire process and look at the entire process for validation.

I think that's what worries me a little bit about the way the studies are being done. I think I would have done the studies the way they're being done. I'm not trying to be critical of the way the study that was presented yesterday was being done, but in light of the results of that study, I think one has to say that alkali and acid by themselves are not going to be enough in that particular experimental protocol, given the way it was done, to get rid of all the TSE that might be there, and so one has to perhaps broaden from that step and now start to say, "Well, let's look at a series of sequential steps and see what they do."

CHAIRMAN BROWN: I think Dr. Rohwer provided us actually with an excellent framework with which to consider processing and validation, and probably everybody on the Committee would not have phrased these questions exactly as they have been phrased because as we have been given information, we may have preferred to have a question, a couple of

questions here.

One is the one that is asked: what are the processing procedures, steps that look most promising for inactivating the agent? That would be one question.

And the second question would be: is there scientific evidence that, in fact, these steps as applied to the processing of gelatin have been shown to do what they might be able to do?

They're really two quite different questions, and you already know the answers. The answer to the first one is steps that involve heat, steps that involve alkaline treatment and to a much lesser degree probably acid treatment, and nonspecific matrix removal steps involved or implicit with filtration and column matrix steps. These are removal steps.

So these are the steps which, in studies using other TSE agents, have been shown to be the most effective.

The answer to the second step is fairly simply no, that there is not sufficient scientific evidence to say that these steps actually do work, at least no scientific evidence yet that these steps actually do work in a procedure which imitates or

mimics the processing of gelatin.

If you would like, we could consider this twin pair of questions separately because I really think they are separate questions. One, we're asked to identify the steps. Two, ultimately we're going to be asked if there's scientific evidence to keep an exemption for gelatin, and they're not exactly the same question.

So why don't we again talk about what steps, if anybody has anything to add, what steps. Are there concerns amongst the Committee members about, one, the kinds of things that should be continued as the industry has so generously offered to do in terms of continuing studies? What kinds of things ought to be being done? What kinds of steps ought to be being tested?

I don't think we have to provide a protocol for the experiments, but at least we might express concerns about the kinds of ways that these studies would be done, certain things that might best be included so that we'd be confident when the results are known.

Anybody? Yes.

DR. WOLFE: Just a comment. The presentations from Kodak and Knox essentially

yesterday, which show that in a country where we do not unfortunately yet have any examples, any BSE infected cow, they are going through all of these steps.

I think part of the logic here, and the reason I asked the question about the connection with the ultimate questions, are we going to continue the exemption, is that I think what we're talking about is even in the best of all possible circumstances, the United States now, where we have no evidence -- it could be latent, harboring some -- we have no evidence. We are pulling out all the stops and doing everything we possibly can at the stage of processing gelatin.

And so if that's the standard in a country where there's no evidence of BSE, obviously that and/or more should be the standard elsewhere.

I'm a little concerned about the part of the presentation we heard from Dr. Schrieber yesterday, was that there didn't seem to be interest on the part of any of the governments in terms of the funding of these kinds of studies. I'm always worried about industry studies that are designed by themselves, carried out by themselves. Aside from the issue of intentions, it sometimes minimizes the amount

of input from others that might do a better job designing studies.

I mean people have been generous to say, "Nice try. You started out well. Too bad you were sort of ODing the first time around," but I think that any subsequent studies should have much more input, if possible could be funded by the government.

And since the second question that I think you correctly pose, is there any scientific validation, is no. We're going to sooner get to the point of being able to at least answer yes or continue answering no if and only if these studies are well designed.

So I think that I would agree fully with your separating it out into two questions, and I would agree that anything that seems reasonable and has a plausible microbiological basis for it should be thought about and added in terms of the first question, what else can we try. Somebody even mentioned solvents yesterday.

But in terms of the second one, we have to rethink how these studies are going to be designed and possibly who's going to pay for them.

CHAIRMAN BROWN: Yes?

MR. FAITEK: It wasn't clear to me that

the processes that were described, although affected in attenuating the transmissible agent, were specifically designed because of that agent. It seems that those are long established processes that have been around a long time, and by coincidence happen to be affected.

And so what I'm saying is that I haven't seen anything on the part of industry that shows that they're making an effort to attack this problem.

CHAIRMAN BROWN: I don't know quite how to deal with this because I and Dr. Rohwer and one or two other people in the room are quite capable of sitting down and talking to you for about two hours about what kinds of studies ought to be done and how they ought to be done. It's not our job, I think, to do that in detail, and I don't quite know how to deal with it.

Would it be legitimate advice to the Commissioner that the Committee strongly recommended that, one, continuing studies of steps for inactivating the agent in the context of gelatin production be evaluated and appropriate validation studies be conducted, and that they engage in conversations with knowledgeable people, such as Dr. Rohwer, to make the designs of such studies convincing?

I mean that's a bit of a cop-out, but I really don't think we can spend two hours at this table designing their experiment for them, but that would be an expression of our desire to see this done.

DR. ROOS: I agree with you, Paul.

CHAIRMAN BROWN: Dr. Roos.

DR. ROOS: Just one other comment, and that is that generally I was encouraged by what seemed to me like a rather extensive processing that goes into making gelatin.

Now, perhaps the reasons for that antedated any concern about the BSE agent. Nevertheless, the idea of throwing this bovine derived material into some vat for -- was it 60 days in lime? -- and a lot of the heat treatments I found encouraging and the little data that we have with respect to validation also suggests that there's some inactivation of the agent as well.

I agree with Paul that I'm certain that there are ways of improving this inactivation and especially, I guess, for the bovine derived products that weren't lime treated or not extensively so. There may be ways of improving things without sacrificing the quality of the gelatin in the final product.

And it's clear from the presentations what kinds of targets and approaches one should pursue with respect to that.

CHAIRMAN BROWN: Yeah, it really is amusing. Irrespective of the TSE agents, if we as TSE people have gone around thinking about what kinds of protocols we might adopt to inactivate the TSE agent, the gelatin process is not a bad approximation as it turns out, which is what you just said.

I mean the only thing that's missing is autoclaving and urea treatment, huh?

So you're already ahead in the race, and it would just be very, very nice to verify the fact that you do, indeed, have a process which will significantly inactivate these agents and to consider, if not, the inclusion of one or more steps which would inactivate the agent.

That seems then -- yes, Dr. Hueston.

DR. HUESTON: May I just reiterate? In the presentation of the process, I think the handling of the raw material is the first step of the process, and I think that perhaps the single most important component of the entire process is that exclusion of heads in plants that are using bovine material where there is BSE in the country or where the country is in

an unknown status.

So the removal of those heads is far more effective in terms of taking infectivity out of the final product, it would appear to me, in a gross sense than any of the inactivation steps.

So we take the heads out first, and then I think there's some other physical components of the process I just don't want to be overlooked as important, the degreasing --

CHAIRMAN BROWN: Yeah.

DR. HUESTON: -- and some of those rinsing steps, as well as those that attempt by either chemical or heat treatment to inactivate the agent.

So if they've got to be taken together, I'd like to re-emphasize that.

CHAIRMAN BROWN: I agree, but in terms of the questions, who designed these questions has, in a sense, artificially but not entirely separated sourcing from inactivating, and what you're saying in terms of, say, for example, taking out the heads, really treads a gray zone in between the two.

DR. HUESTON: Absolutely.

CHAIRMAN BROWN: So, yes, they really are a continuum rather than really terribly discrete considerations.

I think that the second question, what criteria should be considered has just been also addressed. They really are two aspects or three aspects of the same consideration, which is inactivation and processing.

So we can go on to the next slide unless anybody has anything else to say about this slide. Yes, Will.

DR. HUESTON: Sorry, but just for the benefit, I think that I certainly have -- it was a new piece of information, very useful, about the degree to which the gelatin manufacturers are participating in ISO 9000, but the ISO 9000 process, as I understand it, and Dr. Riemann certainly is attempting to emphasize, is a set of international standards for presenting and then documenting the degree to which you are continuously applying the same process on a consistent basis in your manufacturing.

And the benefit of that is that there are records kept. One has record keeping requirements and documentation requirements so that at the very least you know that what is being told to you in terms of the process is actually happening, and I don't think we should minimize.

That fits very nicely in the processing of

validation because then one can translate it back in to say: here's the experimental work that looks at either one part of that or the whole process, and that can be verified, if you will, by this ISO 9000 process to check to make sure that that process is, in fact, implemented at the industry level.

DR. O'ROURKE: Dr. Brown.

CHAIRMAN BROWN: Yes.

DR. O'ROURKE: In fact, I found this question to be one of the most worrisome because I wasn't sure yet how we're defining "inactivation." We've had some discussion about the advantages or disadvantages of mouse adapted scrapie versus BSE and which is the recipient species and which bioassays should be done.

So at the time these studies are being developed, particularly if some are being developed in the United States, as well as in the European community, it would be nice to see some very active discussion and some kind of a consensus on which types of studies will be acceptable.

Since any study takes two to four years to perform, it would be nice to know that at the end people aren't going to stay up and say, "Well, that was the wrong mouse. Let's do it again."

CHAIRMAN BROWN: Well, I'm open to reopening that issue, but it's a very complicated issue. Dr. Rohwer took 30 minutes to --

DR. O'ROURKE: Yes, sir, and I wasn't implying that we should discuss it at this point, but in the context of your suggestion that people should continue to put lots of careful thought into designing these studies before they're performed so that there's somewhat universal acceptance of the findings two years later. The design of the bioassay is critically important in my opinion.

CHAIRMAN BROWN: Right. I agree, and I don't know if it would be appropriate, for example, for the gelatin manufacturers in this country to run these protocols past somebody in government.

Is that inappropriate or appropriate? That is to say, this Committee.

DR. HELLMAN: Being an employee of USDA, I'm sure that I want to be excluded from those discussions. I think that the gelatin manufacturers will call upon the somewhat limited number of experts in the field, as well as people that are experienced in analogous fields in order to come up with a design that's acceptable.

CHAIRMAN BROWN: I was just saying, Dr.

Hellman, I asked that question for partly selfish reasons. I'd love to see such protocol, of course, before it's carried out, but I don't require to see it. I just really was asking whether it is legally appropriate, for example, for that to occur.

Dr. Hellman.

DR. HELLMAN: Yes, it's perfectly appropriate, and that is done.

CHAIRMAN BROWN: Well, this is something that the gelatin manufacturers might take under advisement then, that the Committee will be interested simply in reviewing the protocols of any experiments on inactivation that they design. It's not a question of us thumbs up or thumbs down, but it would certainly be nice for us to see it, and I'm sure that it would be nice for you to know that we've seen it and like it.

Can we have the next slide, please? I think we can probably go beyond it. Well, I think we can. We've just -- at least I've expressed an opinion. If there are any other opinions, I think we've really considered this as well.

DR. HELLMAN: Excuse me, Dr. Brown.

CHAIRMAN BROWN: Yes, Dr. Hellman.

DR. HELLMAN: I just wanted to clarify

it's perfectly appropriate for the FDA to review protocols and to meet with industry. I just wanted to make sure that there was no misunderstanding there.

CHAIRMAN BROWN: Is there a formal distinction between this Committee, which is employed by the FDA, and the FDA that you just mentioned? That is, it's appropriate for the FDA to. Is it appropriate therefore --

DR. HELLMAN: Yes.

CHAIRMAN BROWN: -- for us to?

DR. HELLMAN: It's appropriate for the FDA to review protocols that are brought to it by the industry, and that is done all the time.

CHAIRMAN BROWN: Okay. So then if you --

DR. HELLMAN: Yes.

CHAIRMAN BROWN: -- whoever it was submitted to, decided that it would be nice for the Committee in toto or in part to look, that would be appropriate as well.

DR. HELLMAN: Yes.

CHAIRMAN BROWN: Okay. Dr. Roos.

DR. ROOS: I guess with respect to this question the issue of the best testing comes up,a nd I agree with Bob's comments that it would be a good idea to have several approaches in examining this, and

I just wanted to reiterate that I think it would be useful to start with BSE material. One approach would be mouse derived BSE strain in mice, and another would be natural BSE into transgenic animals of varying sorts.

My guess is that many of these experiments are probably ongoing, and that we will have some data from noncommercial sources about that, but I think that information will be useful, and it will be useful also to examine infectivity of skin from the natural animal as well, just so that we really have that hard data.

CHAIRMAN BROWN: Yeah, and there are certain simple things, as we just were treated to. I mean it's quite a different matter to start with chunks than it is with a homogenate. I mean these are all things starting from A to Z that you have to consider and decide, and it's not any given one experiment that's going to give us the answer. It is, as Dr. Rohwer said, the convergence of results from two or three different kinds of experiments.

And I think we can all say that one experiment that will not be done is a full dress experiment using cattle assayed in cattle. I mean we have to back off from the ideal. That's understood.

The next slide --

DR. DECKER: Dr. Brown.

CHAIRMAN BROWN: Yes, Dr. Decker.

DR. DECKER: I agree that it's always nice to have all of the biological data to do this and understand these steps better, but to do these for a minimum of two years down the road, and I think there's some other ways that you can do process validation and require that that can help in the meantime.

You know, they could do measurements of the efficiency of the degreasing step. They could do validation. They could do the ISO 9000 or the ISO 2000, or we could require that of plants that make gelatin to validate that they are, indeed, doing the processing and maintaining the conditions that have been discussed here.

CHAIRMAN BROWN: Yes. So in other words, you're saying that the state of the art today -- what you'd like to know that it, in fact, is being followed.

DR. DECKER: Right.

CHAIRMAN BROWN: Yeah. The next slide now. No, that's the one of Dr. Asher's presentation slides. What I really want is Question -- I'm sorry.

I'm sorry. I'm sorry. You're absolutely right. So it was the slide that you put up that we want, number 1.2, sourcing. That's right. That's right.

So this begins to get us to the bottom line, and what it says is let's just say we're not going to exempt gelatin. If we did not exempt gelatin, what kind of restrictions would we consider to reduce the risk, and of course the catch word in this sentence is "appropriately."

Nobody knows what "appropriately" means. The sense is to a level that would render any risk negligible.

And the possible options are listed. I think I'll give the Committee about 30 seconds to look at those options and get a reading about them.

DR. DETWILER: Paul, may I add one?

CHAIRMAN BROWN: Dr. Detwiler.

DR. DETWILER: May I add one more option here?

CHAIRMAN BROWN: Sure.

DR. DETWILER: And maybe this fits in with the third one, from establishments in BSE countries, but it's a little bit different. To source from countries not only that or to source from countries that have not reported BSE, but do not have high risk

factors associated with the possibility of having BSE.

CHAIRMAN BROWN: Can you --

DR. DETWILER: In the surveillance.

CHAIRMAN BROWN: Can you rephrase that?

DR. DETWILER: Yeah. To restrict gelatin from countries where BSE has been reported, as well as from countries that have known risk factors and no surveillance systems in place.

CHAIRMAN BROWN: So you would be grouping countries with, say, a few BSE cattle with countries that have not reported BSE cattle, but not surveillance system that would be --

DR. DETWILER: Right.

CHAIRMAN BROWN: -- sufficient to detect them.

DR. DETWILER: Because if you have all the risks but you don't look for it --

CHAIRMAN BROWN: Yeah.

DR. DETWILER: -- you don't have it.

CHAIRMAN BROWN: Okay.

DR. SCHONBERGER: Paul.

CHAIRMAN BROWN: Yes.

DR. SCHONBERGER: I was wondering if we could punt on this a little bit and let the USDA Committee --

CHAIRMAN BROWN: We've already punted on the first two.

DR. SCHONBERGER: Yeah, I know.

CHAIRMAN BROWN: We punt on the three and just get to number four, huh?

DR. SCHONBERGER: Well, I think that's because of the complexity of some of the issues here. I was thinking that if we start to get very specific about what each country's required that we might get into making poor decisions, and I was wondering if USDA could not develop some criteria for the risks of various countries combining, you know, not only the reporting of cases, whether there's compulsory notification, whether there's compulsory clinical and laboratory verification of suspected cases and some qualification of their -- some categorization of their surveillance system, and then based on that develop some type of risk for a country.

CHAIRMAN BROWN: Yes. I'm not personally embarrassed if the Committee were to say, "Look. Here is what the questions are. You're asking us to provide responses to questions for which we don't have adequate information to make a good response."

And I agree with you, as I agree with the USDA members here, that the whole question of source

materials and categorizing or classifying countries from which gelatin is imported makes sense.

Ray.

DR. ROOS: I'm kind of reminded that the WHO suggestion, which was, as I remember it, to get a safe source, which perhaps maybe really is what you're saying. It's not that we want something safe, and I think it probably has to be individualized, and perhaps the best people to really provide those kind of criteria would be USDA, which I guess they're probably working on at any rate because it's important for a variety of points of view.

And if you get too detailed about how many cases there are and whether they're in indigenous cattle and what the surveillance system is and so forth and so on, it gets very complicated.

It seems to me that we're in this bind in which we need bovine derived products for certain kinds of materials, such as these capsules, and the best source seems to be European, and so I think if we want to be realistic about this, as well as feel comfortable, perhaps it's good to provide or get a safe source, and maybe to use the USDA for guidance with respect to that.

CHAIRMAN BROWN: Yeah. Maybe I can

provide a little anecdotal framework of what we're really trying to find an answer to. The extreme would be would we accept to be treated over the course of a year with a kilogram of gelatin based lotion for psoriasis if the gelatin were known to come from a BSE infected cow.

The answer is no, probably. Everybody at the table would demur from being so treated.

The other extreme is would people around the table be willing to take a pill encapsulated with gelatin from a healthy cow coming from France. The answer probably is yes.

Somewhere in the middle, like eating 15 bowls of Jello a day from a healthy cow in England would be something inter mediate, and we're really being asked to say where on this scale of danger or safety we're going to stick.

And so I just wanted to kind of throw that out. That is really what we're talking about. I mean, we're phrasing it in different ways, but we're trying to establish criteria which will allow us to be comfortable.

Dr. Hueston.

DR. HUESTON: May I build on that a moment? I think that obviously we're dealing with a

very complex problem, and we've been given considerable information over the last day and a half. It looks like we can come up with some type of relative risk scale, given your example.

For instance, I wonder if you would follow that the highest risk of gelatin, if there is a risk, the highest risk would be bovine ossein, bone derived gelatin produced by the Type A, the acid procedure, in countries that have BSE or where the BSE status is unknown, and that material then be used in pharmaceuticals for parenteral application. One end of the scale.

At the other end of the scale would be gelatin derived from pig hide splits from the United States used in food applications.

I'm just trying to continue yours and put that scale.

CHAIRMAN BROWN: Yours is a little less picturesque, but it's just as accurate.

DR. HUESTON: Yes. I think though the point would be if you were to use your same example, if you said your example was gelatin used in cosmetics that was derived from bovine hide splits processed by Type B, even if that was from European countries in which there was BSE or the BSE status is unknown, I

think you would get quite a variation in opinions around the table.

I think that's relatively low risk, and in that scale that we just laid out, that's pretty darn low risk material.

So I think it's important as we weigh all of this that we really focus on that relative risk, if you will, and maybe begin sorting out some parts that we want to focus on.

CHAIRMAN BROWN: Let's do it.

Yes.

DR. WOLFE: Many times in the past the FDA has had to make regulatory decisions based on a worst case scenario, which might be 30 bowls of Jello a day, so that within all of these levels there are quantity variations, as well, and since there is no way mainly of controlling what happens in these worst case situations within each of these strata, I think that the decision really has to be extremely cautious.

This whole discussion is obviously predicated on -- I believe it is predicated on -- the answer to the first question, being that the exemption is no longer going to apply, but -- and these are a series of "buts."

I think that the easiest one, although

it's got a little bit of false negative built into it is restrict gelatin from all countries on the USDA BSE list. As Dr. Schonberger pointed out yesterday, if you don't look you don't find, and the question was just raised by Dr. Detwiler also that we have this false sense of security from a number of countries that may have risk factors from having imported British cows or whatever and don't have any kind of surveillance. I think that at the very least we might urge USDA to set up some very strict surveillance criteria that at least have to be applied in those countries that want to continue providing materials for gelatin or whatever else comes in here.

I mean it's interesting to me to think that this is an exemption which means, by definition, that other things from those BSE countries don't come in, and so we are saying: why is not okay to eat other things, mainly eat other things in these countries, but it is okay to eat gelatin?

So it is a complicated question, and it could be made so complex that we could never finish answering it, but I think we could come up with some recommendations that make sense within this issue of spines and whatever. It seems to me that it is more complicated, to be sure, but the idea of really

getting the spines with the cord in out before you start slicing the cows in half, cutting the heads off, and so forth, would be an element that should happen here and everywhere else.

I think we can probably pick off something from this list of options that is reasonable, makes sense and defines what we mean by lifting the exemption.

CHAIRMAN BROWN: That is what we hope to do, but even as you see, the WHO backed off specific suggestions and simply said sourcing should be as safe as possible. It's awfully easy to say that. We all know that. We all agree about that.

DR. WOLFE: That's not good enough.

CHAIRMAN BROWN: That ain't good enough, no.

DR. WOLFE: That's not good enough. I agree.

CHAIRMAN BROWN: And so what we are now in the process of doing is trying to see if we can move a little bit beyond that, and I agree. If there is opinion and comment around the table for any specific recommendations that we can pass on to the Commissioner, he would certainly appreciate it.

Yes, Dr. Faitek.

MR. FAITEK: The suggestion that we use products from countries that have surveillance systems or no established risk goes to the question of the USDA BSE list. What we're, in effect, saying is modify the criteria to be on the BSE list.

CHAIRMAN BROWN: Yes.

MR. FAITEK: That's what we're talking about.

CHAIRMAN BROWN: Exactly, yeah. Dr. Hueston and Dr. Detwiler and Dr. Schonberger and Dr. Wolfe all agree that that is what we would like to see, a review and a reclassification of what is considered a BSE risk country versus what is not.

Granted that this will not be a 100 percent perfect separation.

Dr. Detwiler.

DR. DETWILER: Yes. This would really just be giving no support to something we've started already within house already.

CHAIRMAN BROWN: Yes, Dr. Roos.

DR. ROOS: Getting back to the head and the spinal column issue, because that is an important once since we're talking about source here and clearly central nervous system has the greatest amount of the agent, I guess I have a question, and that is: what

is that head and spinal column good for?

Is that used at present for something that is going to be a problem if we just decide or make a recommendation that part of slaughtering processes for cattle should be removal, especially from areas that have any risk factors for BSE? If we make a suggestion that the head be removed as well as the spinal column, what's the problem? What's the toll that we have to pay as a result of that?

Clearly Britain has adapted that at present, and we see at least a major practice with respect to feeding of cattle being changed over the last decade. So I'm kind of throwing that question out at the moment, whether it's a realistic possibility that slaughterhouses, for example, in Europe would uniformly change their practice with respect to house the carcass is handled.

CHAIRMAN BROWN: I can say a couple of words about that, and other people may want to say something.

So far as I know, and correct me, anybody, if I'm wrong, the head has the tongue, which is an edible product, and at least in calves, it has the brain, which is an edible product. The rest of the head fundamentally is bone, and I guess from what

we've heard, that is chiefly used, if not exclusively used, for the manufacturer or in the past has been included for the manufacture of gelatin.

Spinal cord, on the other hand, it's quite interesting. Don't ask what goes into sausage, for example.

DR. ROOS: Is that still true?

CHAIRMAN BROWN: Well, it was true in England, for sure. Low end hamburger, for example, frequently had filler that included spinal cord.

Spinal cord, as I understand it, is generally used in mixed meat products. If it's used at all, that's where it winds up, and if anybody has any further information about that, yes, Dr. Decker.

DR. DECKER: Well, the spinal cord would be purposely added to the product. It would come through as a carry-through of a process like a mechanical deboning operation.

CHAIRMAN BROWN: Well, apparently in England it was deliberately used as filler.

DR. DECKER: Well, but there should be no real reason why, prior to the processing of the bone for whatever reason, the spinal cord cannot be used, cannot be removed. The technology is available to do that.

CHAIRMAN BROWN: I'm sorry. I didn't follow that.

DR. DECKER: There's no reason --

PARTICIPANT: For gelatin, you mean?

DR. DECKER: -- for any use of the bone, of the backbone. There's no reason that they can't be required to remove that spinal cord. The technology is available to do that.

CHAIRMAN BROWN: Oh, sure. You can get rid of it. I'm just saying that it has not -- in the past when it has not been gotten rid of and when it has been used, this has been the use to which it has been put.

DR. DECKER: But to Dr. Roos' question, I think it is --

CHAIRMAN BROWN: Technically it's a practical matter, yeah.

Dr. Detwiler.

DR. DETWILER: Yes. Can I ask Dr. Roos? Were you referring just in certain countries or recommendation no matter where it's sourced?

DR. ROOS: I was referring to certain countries.

DR. DETWILER: Okay.

DR. ROOS: For example, it's not clear to

me in the United States that it would be a particular important aspect, but in certain countries in which there are risks of BSE or BSE is present, I'm raising that up as a possibility.

In fact, you could still get the tongue out, as well as the brain, but you'd cut the head off first and remove that and maybe just sacrifice the spinal cord as well.

Now, I'm just suggesting this. Has the USDA thought about those as suggestions?

DR. DETWILER: Yes.

DR. ROOS: In a more uniform way than it is now?

DR. DETWILER: Yes, we have, and what we kind of were trying to stay away from, and that's why I asked this, is to clarify, is that the countries that are really making efforts to take all the precautions, even Australia and New Zealand that are going to feed bans despite no evidence of animal TSE, Argentina, et cetera; to paint everybody with the same brush -- because then what happens if you paint everyone with the same brush despite all of the efforts, then you create waste products.

CHAIRMAN BROWN: Dr. Roos.

DR. ROOS: So in a way there may be some

benefit to leave some of these details with the USDA.

CHAIRMAN BROWN: Absolutely.

DR. ROOS: In the sense that there's a lot of individualization.

I have one other little aspect here that's a bit different, and I don't know also how realistic this is, and it has to do with the fact that parenterally administered material is a greater risk, and specifically, I guess, this whole issue really came to the surface with respect to vaccines and the possibility of dangers involving vaccines, especially because one's dealing with a younger age population.

And we did hear that in a way most vaccines, the great majority of vaccines, all have gelatin that is porcine derived, and I guess the question comes up in my mind: why isn't that true of all vaccines now, and whether it would be appropriate for that to be instituted? That is, that generally vaccine companies be urged at this point in time to change to porcine derived gelatin product so that we at least remove this particular risk factor just because the route of administration makes things a bit different because there's a heightened risk.

CHAIRMAN BROWN: Yeah, I don't see any reason why, for example, the whole question of gelatin

couldn't be made into a two or three-tier system, that is to say, gelatin either divided along lines of Type A or Type B gelatin or, perhaps more appropriately, divided along the lines of oral versus parenteral use, oral versus non-oral use.

You could categories countries, for example, BSE positive or BSE negative. You wouldn't use positive or negative. You'd simply designate countries as being appropriate countries from which products for oral consumption are satisfactory or from which products for parenteral consumption could be satisfactory.

I don't generally like to split things up too finely, but it seems to me that kind of a split would be a logical split.

Yes?

DR. ROOS: In a way I'm sure that there's going to be far less control for these oral products. In other words, if some country has gelatin made from bovine derived products, puts it into a food, it's just not clear to me that we're going to be able to regulate importation of this product and be able to figure out if it says the ingredient is gelatin, where it's actually coming from.

I mean maybe I'm wrong about the extent of

the regulatory capabilities here, but that sounds like it's probably not going to happen.

On the other hand, with the vaccines, we have to have approval of that vaccine for its use in this country, and we could have statements and descriptions as to the origins of the gelatin, and I'm just wondering whether because of the parenteral route and because mostly these vaccines are already porcine derived gelatin, whether it might make sense to have a transition time and an urging of particular pharmaceuticals to move over to porcine derived gelatin.

Maybe the FDA has some comments on that, whether that's reasonable and considered.

DR. ASHER: We've had similar thoughts.

CHAIRMAN BROWN: Would it be appropriate then for us, again, to put as part of the written record that this Committee looks to the Department of Agriculture for guidance on a reclassification of countries from which we import either bones or gelatin in the context of risk.

DR. DETWILER: I agree with that. I just want to make sure. Is that with FDA? I mean is that appropriate for human?

CHAIRMAN BROWN: Well, we're not looking

for a regulation now, Linda.

DR. DETWILER: Okay.

CHAIRMAN BROWN: We're looking for guidance. In other words, for us to answer this question, we would like guidance from the USDA for a more modern, realistic classification of countries.

DR. HUESTON: So, in other words, you're saying a classification that might be, for instance, confirmed BSE in the country, another category being the status of the country is unknown, but risk factors are recognized. A third category, there are no risk factors and there's surveillance in place, and maybe a fourth category, there's risk management and prevention measures and surveillance, something like that?

CHAIRMAN BROWN: Yeah, something along these lines with respect to gelatin of Type A or Type B, or with respect to gelatin used orally or non-orally because, let's say, Category 2 could easily very appropriate for oral use, but you might have a qualm about injecting it.

DR. DETWILER: I think with the USDA versus getting us into the details of oral versus parenteral, I think we could come up with categories for everything that we import. You know, the country

is known to exist versus high risk with no surveillance, et cetera, for tiers, and then I think it might be appropriate then for the FDA to make or this Committee to make recommendations on it.

CHAIRMAN BROWN: Yes, Dr. Honstead.

DR. HONSTEAD: Rather than trying to decide what the agencies can do here, I propose that you make the recommendations the best way that you see it, and the agencies will take this as advice. I don't think those decisions can probably be made here.

CHAIRMAN BROWN: Right, just as we cannot now decide precisely what is a listing of risk free or risk promoting countries. What we can do is ask for guidance and direct those other agencies to provide information to allow these questions to be answered.

It would be very nice to answer them all. I mean, it really would, but I think after two days of talking we're all very aware that the caveat at the very beginning that there were substantial porosity to our knowledge, has become very evident to everybody, and specifically with respect to these two questions.

I mean, we've been dealing with processing questions, validation questions. We simply do not have enough good information to give you answers, and in terms of sourcing, we don't have enough good

information to give you answers either, but these answers ought to be available, if not now, in the near future, and in terms of processing, probably within the next year or two.

Yes, yes.

MS. HARRELL: As I sit here representing the consumer interests, I'm very much aware of the public's trust in the FDA to insure that those products regulated by them are safe to use, to consume in whatever form, and for that reason I propose that we cast a broad, wide net that would probably include some of the countries that are low risk, but I think that to insure the safety of Americans, that we should cast that broad net to include restrict gelatin from all countries on the USDA BSE list.

CHAIRMAN BROWN: Okay, and that may well be what ultimately happens. The point is that that BSE list is a list that is now, and what we are asking for is that they look again at that list to see if it can be made somehow more relevant to the risks as we understand them now.

So, yes, that may be done. We won't do it probably, but the BSE list as it now exists is imperfect.

MS. HARRELL: Right, but I think that

there should be no less consideration for the human consumption as it is currently with the USDA's restriction of gelatin for animal consumption.

CHAIRMAN BROWN: Dr. Detwiler.

DR. DETWILER: Would it be appropriate now at least to consider that, that we do know there are some things that are absolutely know? We do know that countries that at least have reported it. I mean that is know.

I mean, is it appropriate to make recommendation at least starting with that and then you can expand it?

CHAIRMAN BROWN: Well, we can consider that. Shall we, for example, lump France, Switzerland, and England? We all know that England is a no-no. Okay? That's one end of the pole. So we use England as a no-no country, huh?

Switzerland is very troublesome because it's got two or 300 cases, and that's troublesome. A lot of them were born after the so-called feed ban, but as I pointed out yesterday, it still doesn't prove that it's indigenous in Switzerland. Still it's showing up in a lot of cows.

France has 20, 25 cows. Probably -- yeah, Will.

DR. HUESTON: Just can I point out the challenge of doing this. I would say from my visits to the countries that Switzerland has the most effective surveillance system of any country I visited. So in a sense, what we're talking about is almost penalizing the countries that have effective surveillance.

If, on the other hand, a country doesn't report it or under-reports, then they appear to be in a much better state than they are. Now, I'm not trying to make any allegations, but suggesting that I think we're on --

CHAIRMAN BROWN: Well, we're talking about France.

DR. HUESTON: Other than saying exists, you know, confirmed in a country where after you get past the confirmed state and differentiating, if you will, the level of the epidemic in Great Britain from the other countries, it's in a tough state.

CHAIRMAN BROWN: Right.

DR. HUESTON: I will mention that France and Switzerland and Ireland, all had their highest number of cases yet last year. I mean they're still on the rise of the epidemic, interestingly.

CHAIRMAN BROWN: Well, this goes along

with what you were saying before. So just to repeat what you said before and now again, yes, put into the formula surveillance.

DR. HUESTON: Right.

CHAIRMAN BROWN: That's what really we're asking. Bring this list updated with every tool that you think is appropriate instead of just saying, "Okay. France has 20. Portugal has 13. Germany has five," and just basing it on a numerical thing. Sure, give us the tools.

Dr. Schonberger.

DR. SCHONBERGER: I just want to add that it may not necessarily be in doing that review that they would have to use country as the unit. It may be appropriate in some instances to break that down into some smaller either geographic unit or even smaller than that, particularly when you get down to the few cases.

Once there's an epidemic going, I think using the country makes a lot of sense, but for example, if there were a case in the United States of BSE, would we really want the whole country classified as being at risk based on one or two cases at that point?

CHAIRMAN BROWN: Yeah, but that -- okay.

Since surveillance, for one thing, is going to be done country by country --

DR. SCHONBERGER: Right.

CHAIRMAN BROWN: -- it's an awfully good reason for maintaining it country --

DR. SCHONBERGER: Oh, you definitely have to start out by country because of that, but the question is once --

PARTICIPANT: Later on.

DR. SCHONBERGER: Later on, after you've got a country classified, particularly if we're talking about a few countries with the small numbers, it might be the sense of this Committee that if they can get down to a smaller unit that makes sense, go ahead and do so.

CHAIRMAN BROWN: Yes, I think you're next, Dr. White.

DR. WHITE: Well, I was thinking somewhat along the same lines, and I think one question that the FDA has put to us is the question about whether we would allow gelatin from certified BSE herds in BSE countries. Somehow that question sort of gets at what you're proposing there, and I guess I'd wonder if members of the Committee would like -- you know, it's hard to address these questions without knowing some

of the things that we'd like to know about validation and so on, but let's suppose there was a valid method. Would members of the Committee -- how would members of the Committee respond to that question about using BSE noninfected herds within BSE countries?

DR. WOLFE: One problem, of course, is the latency period. We can't detect the herd which has latent BSE until they become clinically evident. I think that ideally if and when better detection methods are worked up, what Larry is talking about might be possible to have subunits within a country, but right now we have entire countries that have no surveillance at all and in which, therefore, we can't be terribly confident that the fact that they haven't reported any cases means that it's BSE free.

So I think that I agree with what you were saying, Paul, which is we need to add the level of surveillance to the existing do you or do you not at this point have BSE cows identified in your country, and some combination of that might allow USDA to come up with something better than what we have.

CHAIRMAN BROWN: You don't mind taking a little heat from the other countries that are going to be mightily offended when you tell them they don't have really -- you know, we're classifying them,

downgrading them because of their lack of surveillance. You'll certainly hear about that.

DR. DETWILER: We get it all the time.

DR. WOLFE: That's the way it is.

(Laughter.)

DR. DETWILER: I do have a comment on the herd thing. From somebody that's worked with scrapie certification, and BSE is even more difficult because right now there's no live animal test. There's no live animal test in a preclinical animal for BSE, and we're a little bit further along with scrapie. Hence, it's not like tomorrow you can declare a herd free of BSE.

With the BSE and with a lot of these diseases, it's absence over a long period of time. BSE, you would also have to know any of your possible feed sources probably for the last ten, 15 years.

So to start off with, if you could start today with a herd knowing that it was not going to receive any possibly contaminated feed source, you'd still be talking probably a ten-year period until you could come up with this certification.

DR. WHITE: Well, no, I agree with that. That's why I was asking the question. I mean I think to a certain extent we're deluding ourselves here. We

have no way of telling whether a cow is infected or not, whether it comes from a certified BSE noninfected country or a certified BSE infected country.

I mean you just don't have the answers.

CHAIRMAN BROWN: Are there further comments? Yes.

DR. ROOS: Just to step back for a minute about what our answers really mean, let's say we unanimously decided that we didn't want FDA or that we wanted FDA BSE restrictions on all of Europe for bovine derived gelatin. What does that really mean?

Does that mean that gelatin that gets imported would have to be certified from these European countries as far as its derivation of bovine material? Would it relate to food that got imported, cosmetics that got imported, or are we just dealing in this kind of philosophical way about what we would like in gelatin?

What's the impact of our last 25 minutes of conversation on the FDA?

CHAIRMAN BROWN: And I suppose we could add to that what would the impact, for example, on U.S. gelatin manufacturers be should a recommendation come out that the importation of gelatin from Europe cease.

DR. ROOS: But it really, I guess, just relates to gelatin importation, I would guess. I mean it's just hard for me to believe that no matter what we decided about restrictions of particular herds, whether in a way it has any real meaning as far as what products with respect to cosmetics and food at least really come into the United States.

In other words, are we really going to be able to restrict what kinds of gelatin use occurs in products used by people in the United States?

Am I making my point clear?

CHAIRMAN BROWN: Well, we've got --

DR. ROOS: I mean there are different levels of this restriction, I guess, and in a way it relates to what the FDA decides to do with respect to the regulations, and it has to do with the different products and so forth, and it could be that a lot of what we decide might be advantageous here, in a way maybe we're fooling ourselves as far as what's really going to end up in foods and cosmetics and use because it's just so widely prevalent in the United States. I would guess it's hard to control.

CHAIRMAN BROWN: I don't know if we can do any detailed answers the more I think about it, but we certainly can express principles, and it seems to me

one of the principles that has been enunciated is that any assessment of risk has to include use, that is to say, what it is being used for.

I mean this is a very legitimate reason to separate one risk from another risk category. So as a principle, we can say that we're not talking globally about gelatin. We are talking about gelatin used for A or gelatin used for B. That's just a principle.

So that we wouldn't say a blanket restriction against gelatin, period, from some country or even from this country. I don't know. We need to hear more from other people on the Committee about these things.

Should we try and hammer out some specific recommendations with respect to restrictions, or should we simply express principles and say we just don't have enough information yet to execute these principles?

DR. SCHONBERGER: Did somebody answer Dr. Roos' question though? You were asking what would be the impact if we should just not use gelatin from this derived from Europe?

DR. ROOS: Well, it had to do with, you know, we're wondering about what herds to use, and

let's say we decided, okay, no herds should be used from those four countries in Europe. It's not clear to me what the implication of that statement will really be.

I mean, does it have to do with the importation of gelatin and use of -- you know, even if you restricted the importation of gelatin, you would still have all these imported foods and cosmetics with unclear --

DR. SCHONBERGER: Yeah, I'm just pointing out nobody has answered your question really. What is the impact?

DR. ROOS: It might be hard, and maybe the best answer is that principles are.

DR. SCHONBERGER: That we're headed for principles.

DR. ROOS: That we're headed for principles, and what we would like as far as gelatin use, and some things are pretty clear. Maybe you could talk about parenteral application of material and where that gelatin should be derived from, and another principle is certain things we should keep away from. For example, it's probably not a good idea to have gelatin derived from Great Britain, and then there's kind of a more gray zone here because it

depends on the risk of the source, as well as the use itself.

It gets a little bit complicated.

CHAIRMAN BROWN: Yes.

MS. HARRELL: I think one thing I've not heard mentioned, when we think about the impact of not using or having less gelatin, say, for the pharmaceutical industry to encapsulate meds., we haven't talked about alternatives or substitutes that could be used in the place of gelatin.

Is gelatin the only thing that can be used for these products? If not, then it's not going to make that much of an impact.

CHAIRMAN BROWN: Yes, Dr. Wolfe.

DR. WOLFE: Yeah, I think that although we might have minor disagreements with the phrasing of the other three questions, although I think the FDA did a fairly good job phrasing them, I think that the first question, the one that we ultimately get to, is really binary because right now there is a complete exemption for FDA's ability to do anything about gelatin coming from BSE countries, and they are saying: should we continue to exempt it or not?

And if not, I think that they are implicitly saying that they are going to decide maybe

with our subsequent advice when they come up with their list as to what this means. I think the details as to how much you're going to ingest or whether it is oral versus parenteral and so forth are important, to be sure, but I'm guessing that FDA was not asking that we decide these.

They are all obviously important, and they are principles upon which FDA itself is going to act, but I think that they follow rather than precede the decision about whether we're going to keep the exemption going.

Just to mention something I mentioned before, the much larger issue -- forget gelatin entirely for the moment -- is whether for all the other things that are currently not allowed in from XYZ countries, whether that list is right or not because if it isn't right, which I suspect it may not be, a whole other decision having nothing to do with gelatin is going to be made.

I mean gelatin is not going to be regulated more than these other things. It's going to be regulated as much or possibly slightly less. So I think that the way that the question that we will get to some time soon is phrased implies that FDA just wants to know whether or not the exemption should

continue or not.

CHAIRMAN BROWN: Would it be fair to say that most of the Committee would agree that the best option listed is restrict gelatin from all countries on the USDA BSE list when that list becomes modern? Well, modern? Better, updated.

I guess not.

DR. WOLFE: Except for the fact that that may take so long that there may be some need for an interim action. We're hearing it's going to take a long time.

DR. DETWILER: You can't just go and designate countries without any criteria. I don't think anybody here -- at least I hope we're not suggesting that, that just we can arbitrarily, because we wouldn't want countries just to say, "Ah, U.S., we don't think you're doing this. So, boom, you're on this list."

DR. WOLFE: And you're on our list now.

(Laughter.)

CHAIRMAN BROWN: Okay. That's not going to be around the corner anytime soon.

DR. WOLFE: It's just the existing list right now.

DR. HUESTON: I think also we need to be

careful to distinguish. Gelatin is a pretty broad term. It incorporates a whole lot of things. I mean everything from gelatins going into manufacturing processes, photographic emulsions. I don't think that -- at least I'm having a hard time putting that in the same category as --

CHAIRMAN BROWN: Yeah, well, that's why we brought up the question of a use, of a use, of a use criterion in it as well.

DR. WOLFE: Well, you're talking about within human use, and he's talking about something that is not --

CHAIRMAN BROWN: Well, that's also human versus nonhuman or human, you know, photographic, I guess. I don't know what --

DR. HUESTON: Well, recognize that the reason that USDA's regulations are quite broad is because sometimes when material comes in, it may come in intended for one use and end up in something entirely different. It fails the quality control somewhere along the line. So that's why in a sense even a gelatin that comes in for photographic emulsions is covered under the USDA's regulations, if you follow my meaning.

CHAIRMAN BROWN: Yes, and as the

discussion continues, the Chairman is becoming more and more confused.

(Laughter.)

CHAIRMAN BROWN: And less and less happy with the results of our deliberations. I hope other members of the Committee feel the same way.

Is there any way we can shake loose from this swamp that we have entered into? Dr. Roos.

DR. ROOS: Now, the USDA, we heard, was working on a list and some further details as far as criteria for what's safe with respect to countries. When is that list actually --

DR. DETWILER: Here's the --

DR. ROOS: What does the timetable look like?

DR. DETWILER: Yeah, this is the process. We've actually started it with sheep material, looking at the possible risk of BSE entering in through sheep material. All right. With some of the experimental work done with BSE orally going to sheep, et cetera, and the fact that ruminant products -- but the process is that you send countries questionnaires. We get them all the time from other countries.

What are you surveillance procedures? What are you laboratory diagnostic methods? How do

you routinely go about this, et cetera? What have you imported? Where has it been imported from? How much? Et cetera, et cetera, et cetera.

And then on a case-by-case -- and you have to do this for the world that you trade wit,h and the countries that don't participate, you don't trade with, sometimes don't even answer that. So that it's not an arbitrary designation on there.

So it depends on the time frame, but it can be -- it's not going to be done like tomorrow.

CHAIRMAN BROWN: Yes.

DR. HUESTON: Can I take a crack at your last question and see if I can put this in some perspective?

You laid out earlier, I think, did a very nice job and reiterated this morning that there are four categories of gelatin in use in the United States. One is gelatin that's produced in the U.S. from U.S. source material. The second is gelatin produced in the U.S. from foreign source material. The third is gelatin produced in other countries and imported into the United States, and the fourth is products coming into the United States that contain gelatin.

If we walk down that list then, I think

that maybe it'll help us focus our discussions. The gelatin produced in the United States from U.S. source materials, the direction our discussion is going is saying we don't have a concern related to gelatin produced in the U.S. from U.S. source material.

The second statement, gelatin --

CHAIRMAN BROWN: Before you go there, maybe we should just, since you've put this category on the table again, get a sense from the Committee --

DR. HUESTON: Good point.

CHAIRMAN BROWN: -- on each one, what we think.

Bill, I know we're not supposed to poll the Committee except for the last question, but is it legitimate to poll the Committee on this sort of thing or not, or do we still want just discussion?

DR. FREAS: Well, unless I'm corrected from my colleagues over there in the corner, as Chair of this Committee, what you think is in the best interest of the public health we will abide by. So if you think the best answer is from polling, yes, we can go ahead and poll.

CHAIRMAN BROWN: What would the Committee like to do? Would you like to take some kind of a -- how would we phrase the poll? Would we say --

actually, why don't I let you continue a little bit and see where we're going and then we can decide.

DR. HUESTON: Suggesting the first category, gelatin produced in the United States from U.S. source material may be our gold standard, if you will, or our comparison group.

We said that gelatin produced in the U.S. from foreign sourced material is a concern, but from the presentations yesterday, it would appear that there are currently in place regulations that limit the introduction of raw material into the United States from BSE countries, and in fact, the report that we had of the countries from which raw materials are currently being imported for the manufacture of gelatin is very limited and includes, if I remember correctly, no countries that currently have or have acknowledged BSE.

Mind you their recommendation stands that USDA expand their current list of BSE affected countries to these other risk categories.

Then the third category -- and that's where it sounds like the most of our --

CHAIRMAN BROWN: Yeah, that's where we get the stick.

DR. HUESTON: -- attention is focused, and

that's the gelatin produced in other countries and imported in the United States, and it sounds to me -- and I'm not trying to put words in anyone's mouth -- but it sounds that we're in a sense moving towards recommending a risk based approach.

And if one breaks this down, this whole process, into, if you will, steps for a risk based approach, we have the country status of origin of the source material. We have the raw material itself. We have the method of processing, and then lastly we have the use to which it's put.

And if I can walk down through each of these, we've spent the most time on the country status and a ranking from known BSE of the highest risk to no known risk factors, a risk management program in place, and effective surveillance being the lowest risk category in the countries, and I'm happy to share what I jotted down.

Then in terms of raw materials, it sounds like we're saying the bovine source material is a higher risk than the porcine source material. That relates to our discussion here.

We're saying secondly that bones are a higher risk than split hides, and then we're saying within bones, skulls appear to be the highest risk

bone material, followed by the spine-backbone, and moving on down with the long bones perhaps being at the lowest risk of this continuum.

So I'm building the model that you're talking about of having each of these factors, and one can qualitatively rank the risk of each factor and put that together.

On processing, I believe it's come out that we feel that the alkaline process that's been described has every evidence of being more effective in terms of an activation than the acid process.

And then lastly, in terms of the use, we talked about parenteral being the highest, relatively speaking, the highest risk category, going down to oral or industrial uses as the lowest risk.

So I believe in a sense you could almost draw it on a flip chart that we've laid out a model to recommend or to give back to the FDA in terms of characterizing the relative risk that relates to this whole area of gelatin.

CHAIRMAN BROWN: Yeah, and in terms of graphics, that would probably -- could be done on a three-dimensional graph. Yeah, right, exactly.

I'm happy with that breakdown, none of which we can answer here. We've already made a

recommendation about processing and validation. We could recommend equally that any restrictions that put in place, if any restrictions are put in place, be based on this kind of risk assessment scheme, and that these are what we consider the most important elements in assessing the risk and allow the Commissioner at his pleasure to make the decision.

We cannot make that decision.

Yes?

MR. FAITEK: It seems to me there is some element of time urgency involved in here. The answer to the Question No. 1, I think, is sort of yes or no. If we include these various other restrictions and caveats, the effect of any decision that we make is going to be delayed for a long time, especially if we're talking about changing the BSE list, because it affects other products, and there are going to be other inputs involved here.

So I think the answer that I think we should be addressing is the question first, and if the answer is one way or the other, then we address these other issues and say either ban the materials from BSE countries, but in the meantime, until we can resolve these other three questions, the ban stays in effect, after which these issues will come into play and the

ban can be looked at accordingly.

CHAIRMAN BROWN: Yeah. Had you been the Chairman, you'd have done it the way they were numbered instead of the way I did it. I just made the assumption that, in a sense, if the answer to the first question was yes, then we would adjourn, and I didn't want to do that.

So we have discussed all the other questions, and I think usefully. Whatever we decide about the first question, we've at least gone through the exercise of thinking about the alternative to our answer to the first question, which we are going to come to very shortly.

Yes.

MR. FAITEK: By time element I didn't mean the time at the meeting here.

CHAIRMAN BROWN: No, no, I understand.

MR. FAITEK: I mean time implementing the regulations.

CHAIRMAN BROWN: Yes. Would any of our not officially voting members from the industry, now that you've heard us for an hour -- have you got any additional comments that you'd like to make to us from the industry?

MR. WISEMAN: This is Jerry Wiseman.

In looking at the beginning of the discussion regarding the various safety factors and inactivation factors in the process, it was clear that there were some opportunities to gain additional information.

However, the data as it was presented, Dr. Rohwer, indicated that there was a substantial opportunity in a sequential way to increase the level of inactivity if it were present. It looked like it was very substantial, and we'd like to reiterate that we're continuing to do studies to validate some of these points.

It's very difficult, as we've all discussed, to get all of these validation studies designed properly, but fortunately, with the help of some people here maybe we'll be able to do a bit better job.

Regarding the raw material, very, very difficult to determine even in a country that's a BSE country that all of the material used in that country comes from that country. It could come from other countries, and particularly in Europe where carcasses and hides are traded back and forth with no restrictions. Very difficult.

And so when we look at the amount of

gelatin that is required by our public for all the various uses, it would be, I believe, nearly impossible to supply the gelatin from domestic sources or other non-BSE sources and still meet all of the needs for pharmaceutical and food uses in this country.

So I think there's some practical applications here, and the risk part of it that we talked about, I think it's a very important one where in the event that there was one animal with a disease, does that really mean that that whole country should not be considered as a possible source.

DR. DETWILER: I have a question to follow up on that. Sourcing out of South America, is that impossible? Like Argentina, more sourcing out of there? Countries that have large cattle populations but don't even -- you know, like Argentina doesn't report scrapie as well.

MR. WISEMAN: Well, at the moment, all of the gelatin that can be manufactured there is being manufactured there. So it's not as if there's a huge amount of raw material just sitting there waiting to be converted into gelatin, just as there was a discussion about Australia and New Zealand. Wonderful that there are no cases, but I mean, there are no

cases in Tibet either, but there are no cattle.

And so the fact is from a practical standpoint, we have to look at raw material availability and quantity.

I think the quantity of raw material that's required to make the gelatin needs is really very huge, and so it really has to be countries that have substantial available raw material.

DR. HOEL: Okay. You're saying that the per capita of cattle in Europe is much greater than the per capital cattle in the U.S., and then also the same with pigs, or are you just talking about where the plants are?

MR. WISEMAN: Oh, production. Are you talking about a capacity standpoint or --

DR. HOEL: Well, I'm sure the British also or the U.K. also consumes gelatin products.

MR. WISEMAN: If you look at the world, from a world situation, the U.K. is relatively small as far as the number of animals slaughtered on the world population. So if you lost that as a raw material source, you do not materially affect the world.

But if you talk about BSE countries in Europe that even have one case, you're really talking

about a huge percentage of the world's capacity that would not be able to be used.

CHAIRMAN BROWN: Dr. Detwiler or Dr. Hueston, could I ask you -- I hope I can ask you that -- to tell us -- and I'm sorry if this was said yesterday and I missed it -- what precisely are the recommendations or not the recommendations, but the restrictions recommended by the FDA for bovine derived materials? Can we just have that stated again?

In other words, if we decide to not continue the exemption, what are we comparing it to in terms of restrictions? What are the restrictions?

Maybe it's an FDA question actually, not an Department of Agriculture. I'm sorry.

DR. DETWILER: Yes, yeah.

CHAIRMAN BROWN: What are exactly the restrictions in place now for nonexempted materials?

DR. ASHER: Just simply that they be sourced from non-BSE --

DR. FREAS: Please use the microphone.

DR. ASHER: Yes. The materials are to be sourced from non-BSE sources.

CHAIRMAN BROWN: Using the list that we have been showing, that is, the restrictions are that nothing can be imported from --

DR. ASHER: No, no, not imported. Use from FDA regulated products.

CHAIRMAN BROWN: Used in FDA regulated products. So if it's an FDA regulated --

DR. ASHER: For the manufacture of --

CHAIRMAN BROWN: If a product is regulated by the FDA, it is currently not permitted to originate from BSE countries.

DR. ASHER: It is not recommended. There are various levels of guidance provided, the most stringent being this prohibition by regulation. This is not recommended, which has equivalent force in demonstrating the intentions and opinions of those in the FDA, but it doesn't have the same regulatory force as something that has been through the procedure of becoming a regulation.

CHAIRMAN BROWN: Okay. So products regulated by the FDA are currently under the, shall we say, onus of being recommended not to come from BSE positive countries.

DR. ASHER: Yes. It's voluntary except in the sense that if there should ultimately be a problem, and someone came forward to claim that a person had been infected by the product and the FDA had provided official guidance recommending to the

manufacturer that they not source from such a source, it would leave -- a clear inference could be drawn that due diligence was not shown by the manufacturer in producing the product.

DR. CHIU: I would like to add a little bit. We have a different level of regulation. For example, if drug products and the drug is extracted from bovine source, for example, bovine insulin or surfactant from bovine lungs, those products which we regulate, we have applications in the agency. Then we can require the source is not from BSE countries, which, indeed, we have done so.

However, there are other products which we do not have applications, such as over-the-counter products, OTC drugs, dietary supplements. We have recommendations to the manufacturers. They do not use the sourcing material from BSE countries.

CHAIRMAN BROWN: Okay. Again, something we forget. The FDA is a product oriented agency, and so it is unusual to be considering something as broad ranging as gelatin. What you're saying is that the products that come under the purview of the FDA, its regulatory function, on a product-by-product basis can either have recommendations made about them or restrictions in the sense of prohibitions used.

And to date, since we're considering gelatin, it's wrong of me to say that the FDA recommends a product not be imported from a BSE country. It might be already.

Is there an instance, for example, in which -- you gave an instance. Are they product which was prohibited from coming from a BSE country, not simply a recommendation, but a prohibition?

DR. CHIU: If the Committee recommends gelatin will not come from the sourcing material from the BSE country, then the products, the OTC product, prescription product, which will have applications, then those products if use gelatins, then we can require the pharmaceutical companies to make sure their gelatins will be from the manufacturers which will not use the material, the sourcing material, from BSE country.

CHAIRMAN BROWN: Right. The implication of that is if we take away the exemption, it provides a great deal of work for you because you have to do now product-by-product evaluation to see whether or not recommendations or other restraints are necessary.

DR. CHIU: Yes. We will then go through our -- we already advise listings in the agency the products containing gelatins, either parenteral or

vaccines or other capsules or tabletting products which use gelatin; we do have inactive reagent lists for approved products, approved drugs.

DR. DETWILER: Paul, may I throw one more confounding or not confounding, but with the exemptions which are in ours, which are gelatin and cosmetics, the other products like glandular products, other organ tissues are actually prohibited by our regs. So if the product is like a dietary supplement labeled as such, it would have glandular material from BSE countries. The USDA regulations would keep it out of this country.

DR. WHITE: Paul, I think what you're saying is it doesn't seem to make sense to have Cadillac gelatin and Ford insulin or Ford other products, not to disparage Ford.

(Laughter.)

DR. WHITE: But it seems to me that whatever is done with gelatin ought to be in conformity with what is currently done with other products that come in from these countries.

I think what everybody around the table is saying is that it's probably time, while you make that change now and you go ahead and bring gelatin into conformity with those other products, that it's

probably time for the FDA and/or the USDA to reevaluate how we look at the places from which these materials are coming.

They need to be graded. We grade everything else. We grade eggs as A, B, C, D, E. We need to grade bovine products as A, B, C, D, E, depending on how they're evaluated, the number of cases of BSE that's in that country, and a variety of other things.

I don't see that we can make gelatin a more stringent product than other things that are derived from cows in other countries though.

DR. DETWILER: But the other products, that's what I tried to say. They're already kept out by our regulations.

DR. WHITE: From countries that are --

DR. DETWILER: That have BSE.

DR. WHITE: -- defined by certain -- and we're talking about whether we're going to define gelatin differently from these other products. I'm just saying it doesn't make any sense to define gelatin any differently than you define anything else right now.

CHAIRMAN BROWN: Well, it has been thought that that does make sense, and that is why it was

exempted, and it was exempted because it was felt that there was so little likelihood of any infectivity being in gelatin that the recommendations about BSE versus non-BSE countries were unnecessary. I mean that has been -- that's why we're talking, because that's what's on the table right now, and that's why we're reviewing the possibility that that needs a change, and what you have just said reflects the fact that maybe it does.

DR. WHITE: Well, I think, again, the way you approached the questions was fine. It did stimulate discussion, but I think what I hear the Committee saying is they're probably going to recommend that exemption be removed.

If that exemption is removed, I'm just saying it doesn't make any sense -- if it's not removed, it's a moot point. If that exemption is removed, it doesn't make any sense to make the criteria for gelatin entry into this country in any of its forms any more stringent than the entry of any other bovine derived product.

CHAIRMAN BROWN: Only to the extent that the source material for gelatin, skin and bones, would be log orders different than, for example, the possible infectivity in a product that came from

spleen or pancreas insulin. For example, if insulin were derived from bovine pancreas and administered to humans, yes, then, of course, that would have a substantially higher risk because of what we know about infectivity in different organs of the body.

The bottom line, I think, here is the exemption is in place because it has been felt on the basis of scientific evidence, such as it is, that the likelihood of there being infectivity in either skin or bones is vastly less than in other tissues. That's why the exemption is there now.

Yes, Ray.

DR. ROOS: I guess the other issue besides the risk one has to do with the practicality issue, which was part of that risk-benefit, I guess, and I agree that the data we have makes us less concerned about gelatin as a cause of carrying the agent compared to an internal organ, and in addition, we're kind of confronted at the moment with the idea that we have all of these capsules around, and that all capsules come from gelatin that's manufactured from bovine material from France, and you know, what's going to happen to the pharmaceutical industry if we decide let's put gelatin in the same category as insulin and we'll prohibit BSE countries from

providing material for the gelatin?

So I guess there are two parts to that risk issue. We consider it a relatively low risk, and at least for certain products it looks like the alternative materials to be used aren't forthcoming at the moment.

So I guess that's part of a quandary now to go over this list and to make recommendations and do it in a safe way and also one that's realistic and practical, and maybe that's why the Committee's kind of stymied at the moment a little bit --

CHAIRMAN BROWN: Yeah, that's a good word.

DR. ROOS: -- in trying to divide up each little category end use.

CHAIRMAN BROWN: I have a sense that I'm sort of flogging a dead horse here, not a dead horse, but a horse that's struggling mightily, and I think --

PARTICIPANT: Or a cow.

CHAIRMAN BROWN: Yeah, a cow, right.

(Laughter.)

CHAIRMAN BROWN: I think we have ended useful discussion of this question perhaps some time ago.

(Laughter.)

DR. WOLFE: Only in retrospect.

CHAIRMAN BROWN: I think that Will Hueston's summary type approach of a few minutes ago would provide a decent framework for the question that we have been talking about, and if no one objects, I would recommend that the Commissioner skip to this from the discussion on questions relating to processing and accept the fact that we are concerned about risk, even if small, and that we would like to see a more accurate assessment of risk brought to bear on any restrictions that might be put in with respect to gelatin if any are.

And with that, I think we will go to the bottom line right now, and that is it. Does current scientific evidence justify continuing to exempt gelatin from restrictions recommended by FDA for other bovine derived materials from BSE countries? The question you have all been waiting for.

Before we poll the Committee on this question, I just want to be sure that the Committee understands that scientific evidence in my judgment is all of the scientific evidence that might bear on it, not just the scientific evidence with respect to, for example, validation studies that are still in progress on gelatin itself.

That is, if a decision were to be based on

that, all of us would have to vote the same way: no, there is not sufficient scientific evidence.

We all know that. That has been amply illustrated. The reason the exemption was initially made was because globally scientific evidence bearing on transmissible spongiform encephalopathies suggested that the risk associated with gelatin coming from bones and skins was so small that even if it came from BSE countries, it was negligible.

So scientific evidence is all of scientific evidence. What processes, for example, what steps in the process used for making gelatin have been shown with other TSE agents to be effective? The various processing steps, the likelihood that they would further reduce any infectivity that would already be minimal.

And I should tell you also now that I have just -- not just, but earlier today -- spoken with the head of the Weybridge group in England, which has been conducting experiments on BSE, and there are two types of experiments being done: one, taking tissues from cattle and assaying the presence or absence of that infectivity by inoculating other healthy cattle, and taking tissues from cattle and inoculating those tissues into mice, a less sensitive assay method.

Both methods to date have not detected infectivity either in skin or bone. I do not know how many animals are involved. I do not know the details, but that from the head of the Weybridge Commission.

So that's why exemptions in the past have been thought to be appropriate. So this is scientific evidence that is perhaps very relevant to the answer to this question, and again, I want to reemphasize that scientific evidence is scientific evidence of any sort that bears on the question of risk, not just what's been done on gelatin that has come from -- on gelatin. It's not just what we've heard that is specific for gelatin. It's the entirety of what we know, which is very imperfect, but we do know quite a lot.

And if there are no further comments, I will now poll all of the people sitting at this table for a yes or no answer to the question shown on the screen.

You were going to be the first one polled anyway, Dr. Faitek. So what is it that you'd like to say?

MR. FAITEK: I would like to answer the question, and then I'd like to elaborate if I may.

CHAIRMAN BROWN: Yes. By the way, the

polling is not just yes or no and pass on to the next. If you wish to say yes or no and then say anything, you're welcome to do so.

MR. FAITEK: My answer would be no. There is no justified scientific reason for exempting gelatin.

I think part of the reason for that is in the processes that were shown, the only effective process in those sequences, and I'm not saying that the other processes are not affected, but the most effective process in that sequence of 30 or 40 steps that go through is the sourcing of the material.

Obviously, if you have clean material, the other processes won't make any difference. The issue is that if you have dirty material, are those other processes good enough, and so I think that limiting the sources is the single best step that we can take to assure safety.

The organism is hard to kill. It's hard to detect. It's hard to diagnose, and it's incurable. the problem is that gelatin is so omnipresent in everything that the risk, even though the risk of a single infection is small, the risk to the general population if we should be wrong in that respect is really very, very drastic.

And I think that there's a precedent that we cannot disregard, and that is the contamination of the hemophilic factor with the HIV and the Hepatitis C virus. I'm not sure that there's a direct correlation there, but there is an analogy, and it would be imprudent for us to disregard that history.

And finally, I'd like to offer a nonscientific opinion, and that is that if gelatin were intended for bovine consumption, it would be banned under current regulations, and I think the perception here is to me, who's an unsophisticated user, that we can ban it for cattle, but we can't ban it for people, and it's going to offer a lot of questions for the consumer who may not be significantly informed on the transgenesis of transmittable diseases.

So for all of those reasons, I vote no.

CHAIRMAN BROWN: Dr. Hueston.

DR. HUESTON: Well, the challenge we face here is to support rational decision-making in the face of uncertainty and provide that information and support or helping to steer policy making. I'd like to walk through, I suppose, in leading up to my response the logic that's behind it.

While it's not proven, obviously the data

is accumulating to support an association between BSE and new variant CJD. However, there's no evidence to date of TSE transmission to animals or human via gelatin. In fact, any number of groups that have examined it consider it to be low risk, very low risk.

However, in the information presented over the last day and a half, it's obvious that there is BSE in source material that the process itself does not fully inactivate, and that the sum of the uses of gelatin can expose humans in a whole variety of ways.

Therefore, there are hazards. There are hazards. There are things that can go wrong. Unfortunately we don't know the risk. We don't know the likelihood that they will go wrong. I guess I'm impressed by the lack of information that we have now to be able to complete a full risk assessment.

We're missing a fair amount of data, I believe, in terms of putting all of this together to get at a full risk assessment. Part of that is an audit trail of exactly the origin and use of gelatin.

And I think, you know, I personally have come to the conclusion that we need to use a risk model in addressing it. I think that by and large the vast majority of the gelatin that's being produced and used is essentially safe, of no real risk.

Unfortunately, from the information that's been presented, there is that small portion, as I stated before. I think the bone derived gelatin using the acid manufacturing in countries that have BSE; that gelatin that specifically then is going into pharmaceutical uses is the area of greatest concern for me, and consequently, I would encourage that the FDA focus on that.

Having said all of that, and here comes the challenge, the practical issues, ideally I am more interested in having an effective system to protect human and animal health than I am to whether or not there's an additional regulation on the books, and if we can achieve that further risk management through collaborative efforts, I think that may well be the more effective approach than attempting to regulate it for many of the very reasons we've seen here in this discussion.

So as a result, I guess I am saying there are some issues that need to be addressed. I'm not convinced that we can't. I believe that we may be able to address some of those without exempting gelatin or without changing our current regulatory status as it relates to gelatin.

CHAIRMAN BROWN: The vote?

DR. HUESTON: In the end --

(Laughter.)

CHAIRMAN BROWN: Oh, you thought you were going to slip out.

DR. HUESTON: Almost. Given the information, that's the challenge, but given the information that we have presented before us, then I suppose I would have to say no.

CHAIRMAN BROWN: Let me ask a procedural question. Can anybody abstain or are we referred?

DR. FREAS: That is correct. We're just polling the members at this time.

CHAIRMAN BROWN: Okay.

DR. FREAS: They can make no comment.

CHAIRMAN BROWN: This is really sort of a --

DR. FREAS: And, you know, yes and no, all answers are very appropriate, but they could have no comment or just --

CHAIRMAN BROWN: If you want to sit on the fence. I just wanted to make -- you don't really have to come down hard on one side or the other with some final thing.

DR. HUESTON: Well, thank you.

CHAIRMAN BROWN: If you'd prefer to say,

"I really don't know how to answer this," I mean all of your testimony, shall we say, is on the record, and if you would prefer not to render an opinion, a yes or a no, to this question that is appropriate.

DR. HUESTON: Then I'll say I think there are some issues that need to be addressed. I'm not sure that we have to proceed with changing the current exemption. You know, I'd be right there on the fence, depending on the processes and the further clarification of the risk and risk management approaches that we could achieve.

CHAIRMAN BROWN: So we could say uncertain.

DR. HUESTON: Yes.

CHAIRMAN BROWN: And before Dr. Detwiler asks or tells us what she thinks, I'm not sure anybody has said this either. If they did, I didn't catch it. What other products are exempted?

Gelatin is exempted. Is it unique or are there other products that are exempted from this?

DR. ASHER: Milk, milk products, talon, talon derivatives.

DR. DETWILER: No, no, no.

DR. FREAS: Microphone.

DR. CHIU: Milk and the dairy derived

products.

CHAIRMAN BROWN: So dairy derived products are exempted, as well as gelatin.

DR. BAILEY: The regulations as they are now written also allow the importation of collagen, collagen products, amniotic liquids or extracts, placental liquids or extracts, serum albumin, and serocolostrum from BSE countries for use in cosmetics.

CHAIRMAN BROWN: Just for use in cosmetics?

DR. BAILEY: Just cosmetics.

DR. WHITE: No, wait a minute. I'm confused by your statement now. You mean all of those things that you just listed only for use in cosmetics or only the last thing that you listed for use in cosmetics?

DR. BAILEY: All of them.

DR. DETWILER: Except milk and milk products.

DR. BAILEY: The ingredients that I read off are specifically applicable to cosmetics. The milk and the meat and so forth, you know, that's a different issue.

CHAIRMAN BROWN: Milk and -- I'm sorry -- milk and meat?

DR. WHITE: Milk and milk products.

DR. BAILEY: Milk, milk. I'm sorry.

CHAIRMAN BROWN: And no products.

DR. BAILEY: Just milk.

CHAIRMAN BROWN: That's kind of a carte blanche, but the others are exempted strictly for cosmetics.

DR. BAILEY: Just for cosmetics, correct.

CHAIRMAN BROWN: Linda Detwiler.

DR. DETWILER: I just want to preface that I'm here to provide information on what the USDA does, but when I vote I do not speak for the Department of Agriculture on this Committee.

Right now on a carte blanche, based on science, I'd have to vote no if it was carte blanche, but my only scientific basis for voting no are the high risk tissues of skull and spinal cord. The skin and long bone, I couldn't find any scientific reason to vote no on an exemption.

So it's no, but with the caveats.

CHAIRMAN BROWN: Is it fair to say also that if we wanted to rephrase Dr. Hueston and you that it's a qualified no?

DR. DETWILER: You be. That's a good qualified no, yes.

CHAIRMAN BROWN: Okay.

DR. DETWILER: Based on the science.

CHAIRMAN BROWN: I try to make my Committee happy.

Dr. Hoel.

DR. HOEL: Yes, I would also vote no on this issue. I think what disturbs me here is that the hazard or risk, if you want to say, can be so great, but yet with such a low probability.

If I envision, say, one bad cow going through the system and spreading that among enough capsules in the population, given that we haven't seen calculations that would show the probability of that reduction in titer to where it would have zero probability or close to it, I worry very much about this, and I have not seen those types of calculations, and this can be, you know, whether it's from these countries or even if spontaneous occurrences can happen in the process, I think we have to pay close attention to the uses of the individual products and, in particular, if bones could be used in industrial products and not in human consumption, and anything you can do to reduce the risk, even though we can't calculate it at this point.

So I think there are enough unknowns and

the risk can be so great that I would say no.

CHAIRMAN BROWN: Ms. Harrell.

MS. HARRELL: Representing the prudent people or the prudent man on the street who if it were known that a product, a food product or a cosmetic, were from a BSE country would not want that product, and with the evidence or the lack of evidence that the processing of those raw materials is not insured to inactivate the agent, then I would have to vote no.

CHAIRMAN BROWN: Dr. Schonberger.

DR. SCHONBERGER: Yes, I vote no, as well. I think it's very likely that the gelatin is safe,b ut I think the data right now is relatively in my mind insufficient for the amount of exposures that are going on. Particularly I'm concerned about the injection of the materials, the parenteral exposures, and I'm also concerned about some of the looseness that I feel in the control of this substance and the existence of what I would consider the more risky material, the Type A bovine derived from BSE countries also coming in in the same way that other products are allowed in.

It just seems a little loose, but again, I think the material is probably safe, but again, insufficient information.

CHAIRMAN BROWN: Dr. Wolfe.

DR. WOLFE: I'd just like to briefly repeat in about 25 seconds the three points made by Dr. Asher this morning, which really explain why we're here and why this vote is important.

One, we now at least are much more worried than we were before that these agents can cross species. The new clinical form of the disease in England is the cause of this concern.

Secondly, there is evidence of residual neural tissue, spinal cord, et cetera, in the materials from which gelatin is produced.

And third, it is clear that we do not have any guarantee in the process of making gelatin that we remove the infectivity.

So I think these are the reasons we're here, and these are the reasons why I'm really compelled to vote no. This material should no longer be exempt.

CHAIRMAN BROWN: Dr. White.

DR. WHITE: Yes, well, I would agree. I would say until we have evidence, scientific evidence, that it should be exempted, it should not be exempted. So I would vote no.

CHAIRMAN BROWN: Dr. Roos?

DR. ROOS: No.

CHAIRMAN BROWN: Dr. O'Rourke.

DR. O'ROURKE: I'd like to see FDA have control over particular gelatin-containing products. As many of you have stated, I'm particularly concerned about parenteral use of products containing gelatin prepared from bovine bones.

If we have to lift this exemption in order to give FDA that use-by-use right, then I would have to vote no.

CHAIRMAN BROWN: I think the risk inherent in gelatin --

DR. RIEMANN: Dr. Brown.

CHAIRMAN BROWN: Yes. Oh, I'm sorry. I beg your pardon? Dr. Riemann.

DR. RIEMANN: I would vote yes and I'll base this on the information, however incomplete it is, on the risk reduction that is associated with the processing of gelatin, but I would also base it on what I would call the epidemiological picture of the PSE, and if you want I can elaborate on that, but my vote is yes.

CHAIRMAN BROWN: Dr. -- if you'd like to elaborate, this is the time to do it because we're closing down.

DR. SCHONBERGER: Yeah, I would like to hear that.

DR. RIEMANN: Well, I won't go back to the beginning because that would take me 100 years back, but it seemed clear to me that the BSE epidemic is on the decline; that the decision that was made in the United Kingdom to stop to feed animal, bovine, products back to the cattle is effective.

The killing and burning of cattle, of course, has no effect on the epidemic.

Until recently, as some people have indicated, there was no or no one believed that BSE could become a human pathogen. Now they've had 16 cases of actual Creutzfeldt-Jakob disease in humans in Britain, but in my mind there is no epidemiological evidence that this is associated with BSE simply because no epidemiological studies have been done. I doubt anybody would like to do a case control study with 16 cases.

The cases are unusual in the way that I understand all are under 40 years. That raises a question why should people under 40 years be the higher risk for getting BSE infection than older people.

These 16 people apparently are the only

ones. All the people working in the slaughterhouses where they have been in contact with hundreds if not thousands of infected carcasses, carcasses infected with BSE, we have no evidence that there has been any transmission through the slaughterhouse workers in spite of close contact.

We know that such transmission can take with all of the agents in the attempt to eradicate swine brucellosis in the United States. Reactors, swine was sent to slaughterhouses with the result that there was epidemics or outbreaks of brucellosis in the slaughterhouse workers.

So, in summary, I think the idea that BSE in the 12 cases of Creutzfeldt-Jakob disease or the 16 cases in Britain should be due to BSE is very slim, and there is no evidence.

CHAIRMAN BROWN: Dr. Decker.

DR. DECKER: I guess if I had a choice of any bovine product to eat from a BSE country, I would probably pick gelatin because it probably is the safest product, but I would like to vote as a qualified yes because I do think it's very important. I don't think that this is a high risk product, but at the same time I think it's very important for the industry to validate the safety of their product, and

especially their product for use in pharmaceutical ingredients.

And so I think it's very important that they continue down that road to validate their processing and to validate their raw materials to insure the safety of their products.

CHAIRMAN BROWN: That is a qualified yes, I think was the expression.

I think that my own vote will be a qualified no, but it is a no, and simply because I think while all indications are that gelatin is likely to be a safe product, I would rather see it put on amber now before giving it a full green again.

I do not think that gelatin is in the same category as milk, for example, which I would absolutely say ought still to be exempted, but I think it is not shown conclusively to be in the same category as this product, dairy products. I think it may well return to this category when appropriate further study has been done or it turns out that these cases of variant CJD in humans may not be due to the exposure to BSE, still a very moot point as Dr. Riemann has indicated, but they could, and there's no better explanation on the table at the moment.

And so I would prefer a more cautious than

a less cautious judgment, and that is the reason for my own answer to that.

I should tell you that Dr. Williams, who is absent, is supposed to send back an answer, and that Dr. Hsiao gave us a qualified yes in answer to that question, with the note that she would like to know whether any gelatin from BSE countries is made from bovine hide using the acid method, but that would not have changed her response to the question.

I think this Committee has now gone through a day and a half, and I would ask if anybody at the table has any final comments to make, and if not, if Dr. Freas has any announcements or comments.

DR. FREAS: I would just like to thank Dr. Brown for the excellent job he did as Chair.

I would also like to thank the Committee members also for their contribution to the discussion. If you do have confidential material that was distributed to you, please leave it on the table so we can inventory it and destroy it today.

My thanks to everybody, and thanks to the audience for attending.

(Whereupon, at 12:50 p.m., the Advisory Committee meeting was concluded.)